JPRS-JST-86-013

14 MAY 1986

Japan Report

SCIENCE AND TECHNOLOGY

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JAPAN REPORT

SCIENCE AND TECHNOLOGY

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BIOTECHNOLOGY

LIFE SCIENCE--PRESENT, FUTURE DESCRIBED

Present Status and Prospects

Tokyo PUROMETEUSU in Japanese Jul-Aug 85 pp 19-24

[Article by Tohru Takahashi, chief of Life Science Planning Division of the Science and Technology Agency Planning Bureau: "Present Status and Prospects of Our Nation's Life Science"]

[Excerpts] Present Status of Life Science

According to the Life Science Research Investigation revealed by the General Affairs Agency Statistic Bureau last December, the total cost of fiscal 1983's life science research amounted to Y742.6 billion, more than 10% of scientific and technological research (Y7.18 trillion.) Its growth trend over preceding years has been steady, constituting 27 percent for fiscal 1982 and 14 percent for fiscal 1983, considerably exceeding that of total scientific and technological research. It included corporations, 45 percent, research institutions, 12 percent, and colleges, 43 percent. As to its purposes, health and medical research constituted 71 percent, followed by basic research for analysis of life phenomena, about 10 percent, food resources, 6 percent, environmental protection, 4 percent, and mining and manufacturing industries, 4 percent.

The personnel involved in life science, on the other hand, amounted to 107,600, about 15 percent of the total involved in research (741,300). This total included 70,000 in colleges, 23,000 in corporations, and 12,000 in research institutions, the first constituting an amazingly high ratio of 65 percent. The researchers working at colleges account for as high a ratio as 73 percent of their total, i.e., three of four researchers are working there. Those engaged in scientific and technological research are distributed among corporations, 56 percent, colleges, 33 percent, and research institutions, 11 percent. Thus, life science still remains primarily in corporations

According to the Life Science Planning Department's investigation, total government life science research expenditures, excluding personnel costs, research costs per head and other ordinary expenses, is estimated at Y45 billion for fiscal 1984, and at Y46 billion, excluding scientific

research subsidiaries not yet calculated (and a little less than Y50 billion including them) for fiscal 1985. It includes about Y20 billion for the Ministry of Health and Welfare, about Y11 billion for the Ministry of Education (scientific research subsidiaries are estimated to be equal to the preceding years), about Y8.5 billion for the Science and Technology Agency, about Y4.5 billion for the Ministry of Agriculture, Forestry and Fisheries, and about Y3.6 billion for the Ministry of International Trade and Industry.

The trend of research in nongovernmental corporations will now be described. In Japan, the fermentation industry has developed from ancient times. Included among the technologies for applying microbes to production processes are the techniques developed by Japanese researchers to produce amino acid, taste-displaying nucleotide, and others. They serve as the basis of the nation's biotechnology; its applied microbiology industry is said to be at the world's top level. At present, nongovernmental corporation life science research and development is rapidly increasing in scale. According to the General Affairs Agency's statistics mentioned above, research and development expenditures grew by 15 percent for fiscal 1982 and 13 percent for fiscal 1983, and the population of researchers increased by 6 percent for fiscal 1983. The construction and extension of research facilities have also rapidly increased. At present, the chemical and food industries are playing a leading role in life science research and development. Since it has a wide scope of application, however, technological development is being carried on by a number of corporations in the mining, electric, machinery, and other industries.

Safety of Research on Recombinant DNA

In life science research it is naturally necessary to give due consideration to safety. Recombinant DNA technology, a key tool, applies to a wide range of basic and applied research. Sufficient care is necessary because the technology creates cells with new combinations of genes that have never before existed in nature.

The Science and Technology Council presented the guidelines for the fundamental requirements of the basic concept on recombinant DNA research as well as its practice and safety in its report in answer to Question No 8, "The Fundamentals of the Measures for Pushing Forward Gene Recombination Research." The prime minister issued the "Guidelines for Recombinant DNA Experiments" on the basis of this report and notified the concerned authorities in August 1979.

The guidelines deal with the requirements of 1) the duties of those engaged in experiments and the heads of laboratories and research institutions; 2) the standards for containment measures to be selected according to the evaluation of their safety; and 3) the organizations for education, training, and health control as well as for securing it. Particularly as to the second requirement, it characteristically refers to the standards for 1) physical containment that requires laboratory facilities and equipment, as well as procedures for experiments, to be prescribed depending on their category (the combinations of the host-vector systems and DNA donors to be used); 2) biological containment on which only the specific host-vector systems

Table 1. Important Targets of Life Science Research

Research field	Research target
1. Life phenomena, organism functions	1. Elucidation of life phenomena, organism functions
2. Natural environment of humans	1. Elucidation of the relationship between human activities and the biosphere 2. Elucidation of the mechanism of the material circulation in the ecosystem
3. Natural science on mental activities	1. Elucidation of perception, activity, other brain functions 2. Research on the reversibility, learning ability, adaptability of the brain 3. Solution of the problems in nervous embryology, genetic psychology 4. Biological and physiological elucidation of the development mechanism of mental diseases 5. Elucidation of the relationship between spirit and body 6. Elucidation of the relationship between social and cultural environment and mental structure
4. Maintenance, promotion of health, improvement of health and medical treatment	1. Basic research on health, nutrition and exercise 2. Medical elucidation of the mechanism of aging at molecular and cellular levels and of aging at organ level 3. Research on mother and child health during cyclic birth period 4. Elucidation of the causes of congenital abnormalities; development of disease preventive, diagnostic, therapeutic technology 5. General research on human heredity 6. Research on prevention, diagnosis, and therapy of adult, mental, nervous, intractable, and other diseases 7. Development of diagnostic and therapeutic apparatuses, artificial organs, etc., by introducing engineering methods 8. Establishment of technology for evaluating the safety of chemical materials, etc. 9. Search for organism-activating materials, development of technology for their use 10. Basic and engineering research on rehabilitation
5. Securing food resources	1. Development of technology for producing and using food resources 2. Securing protein resources, developing of its utilization
6. Energy issues	1. Development of technology for producing plants, etc., useful as energy resources and for their conversion by utilizing microbes, etc. 2. Elucidation of photosynthesis mechanism, development of its utilization technology
7. Industrial utilization of organisms, their functions	1. Development of technology for industrial utilization of organisms, their functions 2. Development of industrial technology for harmonizing human and other organisms
8. Problems of population	1. Research on harmony between environment resources, and population 2. Research on endocriminology, other reproductive biologies in broad sense
9. Recombinant DNA	1. Research on safety evaluation 2. Development of safe, useful host-vector systems 3. Development of technology for analyzing and synthesizing DNA 4. Elucidation of mechanism of manifesting different kinds of genes 5. Development of technology for producing useful materials, efficiently utilizing microbes and enzymes by applying recombinant DNA technology

Source: Science and Technology Council, "View on the Promotion of Life Science" 19 August 1980)

Table 2. Transition of Research Costs by Institutions

Division	Fiscal year	Total	Corporations	Research institutes	Colleges
Value (Y100 million)	1981	5,099	2,558	552	1,989
	1982	6,492	2,944	840	2,707
	1983	7,426	3,348	859	3,220
Growth over previous year (percent)	1982	27.3	15.1	52.2	36.1
	1983	14.4	13.7	2.2	18.9
Ratio to total cost (percent)	1981	100.0	50.2	10.8	39.0
	1982	100.0	45.4	12.9	41.7
	1983	100.0	45.1	11.6	43.4
Ratio to science and technology research cost (percent)	1981	8.5	7.0	6.1	13.8
	1982	9.9	7.3	8.9	17.6
	1983	10.3	7.3	8.8	19.5

confirmed to be safe can be used in the experiments; and 3) the containment (the combinations of physical and biological containments) suitable for their categories.

The guidelines have hitherto been revised five times to reflect newly-accumulated knowledge, foreign trends, and so forth. Guidelines for mass-culture experiments were published in September 1983. Further revisions should be made in consideration of industrial ones.

Prospects for the Future

In the future development of science and technology, it is significant to establish their new relationship with humans with importance attached to the latter. The guideilnes emphasize the necessity of promoting research in human science and technology for totally understanding humans themselves, particularly for "placing importance on elucidating the mechanism that characterizes them."

Included among the research in human science and technology is research on the brain and nervous system that supports the high-order mental activities for recognition, sentiment and action, and creates "human heart," and research on immunity as a biological function for protecting an individual's totality by purging "nonself" distinguished from "self." As move of the population is living longer, research on human aging would be included among the subjects in this field.

Molecular biology methods that have supported the latest progress of life science have contributed to mankind's elucidation of hereditary diseases by the fundamentals of hereditary phenomena and provided it with the technology

for breeding new organisms. New-generation life science provides advantages to various sectors of human society, e.g., contribution to the curing of senile dementia and other diseases in which the brain is concerned, development of high-order artificial intelligence and new education methods, and prevention of intractable diseases by elucidating the high-order functions peculiar to humans. Human science and technology are included among the important subjects of future life science.

In the course of the latest progress of life science, for example, no consideration can be disregarded concerning the problems of how organ transplantation and external fertilization should be connected with human dignity, ethics, and the philosophy of living and thinking.

The Science and Technology Council's No 12 Report cites "the development of science and technology in harmony with humans and society" among the most important tasks of their policies. It continues "It is necessary for a wide range of those concerned-research, technology application, planning, and promoting sectors--to examine these matters." The council will soon start examination to this effect.

Careful consideration has been given to matters in the research on life science since it deals with organisms, particularly humans. It is necessary to continue efforts in this direction in the future also.

Science and Technology Agency's Life Science

Tokyo PUROMETEUSU in Japanese Jul-Aug 85 pp 24-27

[Article by Eiji Urushibara of the Life Science Project Section of the Planning Bureau, MITI: "Promoting and Regulating Fundamentals of Scientific Technologies"]

[Text] The report in answer to the government's question No 5 "Fundamentals of 1970's Comprehensive Scientific and Technological Policies," issued in 1971, used the term "life science" for the first time in Japan. The report included it among important scientific and technological sectors to be promoted by the government in the future. In this direction, the Science and Technology Agency established the Life Science Planning Room in its office in 1973 and the Life Science Promotion Division in the Institute of Chemical and Physical Research in 1974.

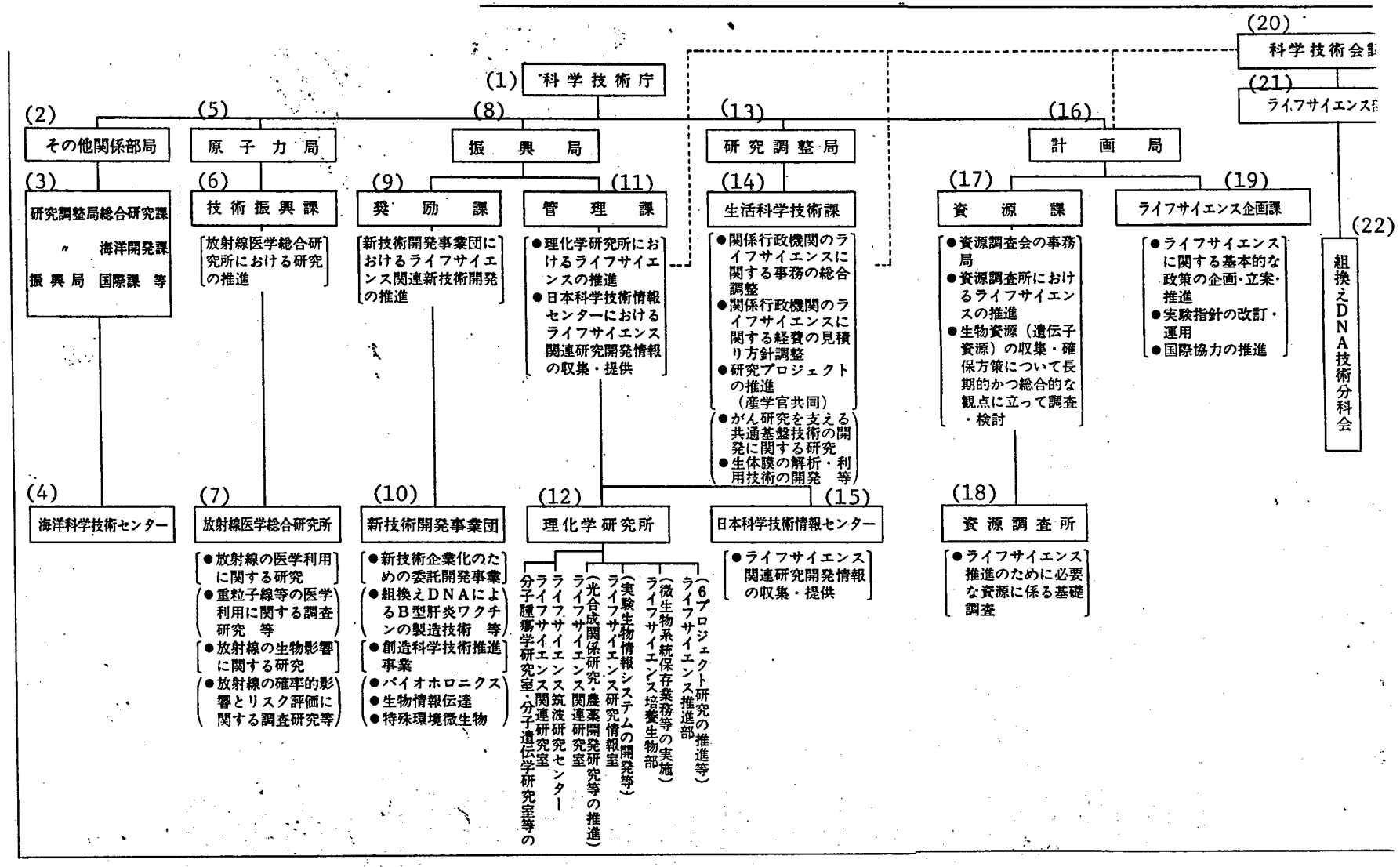
At present, the institute takes the following various measures for promoting life science on the basis of the report:

(1) Formulation of fundamental policies, planning and promotion of research;

(2) Promotion through consolidated coordination of the respective ministry/agency;

(3) Promotion of leading and basic research;

Science and Technology Agency's Life Science Promotion System



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[Key to Science and Technology Agency's Life Science Promotion System]

1. Science and Technology Agency
2. Other sections concerned
3. Research Coordination Bureau, Comprehensive Research Department, Ocean Development Department, Promotion Bureau, etc.
4. Ocean Science Technology Center
5. Atomic Energy Bureau
6. Technology Promotion Department (Promotion of National Institute of Radiological Science's research)
7. National Institute of Radiological Science
   (• Research on the medical application of radioactive rays)
   (• Investigation, research, etc., on the medical application of heavy particle rays)
   (• Research on the biological influences of radioactive rays)
   (• Investigation, research, etc., on the probability influences and risk evaluation of radioactive rays)
8. Promotion Bureau
9. Encouragement Department (Promotion of Research Corporation of Japan's development of new technology related to life science)
10. Research Corporation of Japan
    (• Commissioned development for commercializing new technology)
    (• Technology for producing B-type hepatitis by using recombinant DNA, etc.)
    (• Promotion of creative science and technology)
    (• Bioholonics • Transmission of informations in organisms • Special environment microbes)
11. Management Department
    (• Promotion of the Institute of Physical and Chemical Research's study of life science
    • The Japan Information Center of Science and Technology's (JICST) collection and supply of the information of the study and development related to life science)
12. The Institute of Physical and Chemical Research
    Life Science Promotion Division
    (Promotion of six research projects, etc.)
    Life Science Culture Biology Division
    (Preservation of microbe systems, etc.)
    Life Science Research Information Room
    (Development of experimental organism information systems, etc.)
    Life Science Research Room
    (Promotion of the research on photosynthesis, development, and study of agricultural medicines, etc.)
    Life Science Tsukuba Research Center
    Molecular Oncology Research Room, Molecular Genetics Research Room, and other life science research rooms
13. Research Coordination Bureau
14. Life Science Technology Department
    (• Collective coordination of the concerned administrative institutions' affairs related to life science
    • Coordination of the principles of their cost estimation
    • Promotion of projects (joint research by administrative, industrial, and academic circles)
    (• Research for developing common basic cancer-study supporting technology
    • Development of biomembrane analyzing and utilizing technology, etc.)
15. The Japan Information Center of Science and Technology (JICST)
    (• Collection and supply of research and development information of life science)
16. Planning Bureau
17. Resources Department
    (• Secretariat Bureau of Resource Investigation Commission
    • Promotion of National Institute of resources' research on life science
    • Long-range, collective investigation and research on the measures for collecting and securing organism resources (genes))
18. National Institute of Resources
    (• Basic survey on resources for promoting life science)
19. Life Science Planning Department
    (• Formulation and promotion of basic life science policies
    • Revision and operation of experiment guidelines
    • Promotion of international cooperation)
20. Science and Technology Council
21. Life Science Division
22. Recombinant DNA Technology Subdivision

(4) Reinforcement of research support system;

(5) Promotion of international cooperation.

Formulation of Fundamental Policies, Planning, and Promotion of Research

The agency's Secretariat Bureau is collecting various reports and opinions regarding life science, and carrying out the revision of, for example, "The Guidelines for Recombinant DNA Experiments," and other jobs connected with the safety of research on recombinant DNA.

Promotion Through Consolidated Coordination of the Respective Ministry/Agency

The agency is carrying out the coordination of the principles for estimating the costs related to science and technology between the authorities concerned in life science.

Furthermore, the agency is pushing forward the research and development in leading and basic sectors at the expense of the "science and technology promotion and coordination fund" founded in fiscal 1981. It includes "study for developing the technology of analyzing, qualifying, and simulating functional proteins," "study for developing the common-basis technology of supporting cancer research," and "study for the technology of research for and utilizing the physiology-activating materials produced by new symbiotic microbes" that are carried out under the cooperation of national laboratories and research institutes, colleges, and corporations. Mentioned among the new subjects of fiscal 1985's research are "study for developing the technology for analyzing and utilizing chromosomes" and "study on the basic technology for elucidating brain functions."

Among the major results achieved under conventional research projects are the establishment of technologies for producing a B-type hepatitis vaccine, a DNA-base arrangement analyzing system, and the artificial synthesization and generation of a human growth hormone gene. The agency held symposiums on them to raise Japan's research level.

Promotion of Leading and Basic Research

Life science research and development is promoted by the Institute of Physical and Chemical Research, the Research Development Corporation of Japan, and the National Institute of Radiological Sciences.

The first institute established the Life Science Promotion Division in May 1974, and started research on five subjects--"the control of aging," "bioreactors," "artificial organs," "intelligent machinery" and "organism-activating materials" under a 10-year project in 1977, and research on "new microbe utilizing technology" under a 10-year project in fiscal 1980.

The institute's Life Science Tsukuba Research Center is constructing a gene recombination experiment and research building with the highest-level

containment facilities as common-use research facilities for collectively promoting recombinant DNA research in Japan.

Lately, recombinant DNA research is attracting the attention of those particularly concerned in life science because it is expected to contribute much to mankind's welfare from a wide range of basic studies elucidating the structures and functions of organisms' genes, as well as applied studies locating the causes of cancer and other diseases, mass producing insulin, interferon and other rare medicines, and breeding useful microbes and farm produce.

The corporation is carrying out "new technology development" centered on the commissioned development for finding the best results of Japanese research and offering the opportunity for commercializing them and "the promotion of creative science and technology" for cultivating innovative scientific and technological fields and developing new creative technology.

The former's subjects include "technology for producing a B-type hepatitis vaccine with recombinant DNA," "an automatic DNA-base arrangement determining system," and "development of the leukocyte-increasing factors of human origin" and the latter's "bioholonics" for securing the harmony in vivo, "information transmission in organisms" for research on and application of information transmitting materials of the brain and nervous system, and "special environment microbes" for handling the microbes growing in strong-acid and alkali and other severe environments.

The last institute has continued the investigation, research, and so forth on human diseases by radioactive rays since 1957 and has already started research on cancer, particularly on the medical application of heavy particle rays and the application of radioactive rays to their diagnosis and therapy.

Reinforcement of Research Support System

Policies are underway for reinforcing life science research support system.

The Institute of Physical and Chemical Research is collecting and preserving microbes useful for research and industry. A supply of about 4,000 stocks preserved at present will be started soon. It is also engaged in developing an information system for experimental organisms, including animals.

The research center has added the construction of cell and gene reserving facilities (gene bank building) to its fiscal 1985 new enterprises.

The Japan Information Center of Science and Technology (JICST) collects, preserves, and supplies the scientific and technological information related to life science. To promote these activities, it has introduced a DNA database and is carrying out the developiment of the system for supplying data and a database of 120,000 life science publications per year.

The Resource Survey Commission sponsored by the director of the agency advised the fundamental direction of the selection, search for, collection, and supply of the organisms to be secured among genetic resources, as well as the distribution of the information connected with them, as well as the measures for their promotion in its report submitted in answer to the Question "On the Measures for Securing Organisms as Genetic Resources" in June 1984. The agency is carrying out investigation for establishing resource organism-preserving measures and the investigation and examination of the measures for collecting, preserving, and using wild animals.

The National Institute of Resources is carrying out investigation regarding the constant supply of protein resources and the sophisticated application of forestry resources.

Promotion of International Cooperation

The following are examples of cooperation in life science between two nations.

Japan and the United States are busily exchanging information regarding recombinant DNA research under the Non-Energy Research Cooperation Agreement.

Japan and West Germany have held biological and medical panel discussion meetings and bio-process technology workshops for information exchange under the Scientific and Technological Cooperation Agreement.

Japan and China are cooperating with each other in the development of physiology-acting materials produced by microbes, as well as experimental animals.

Japan is also carrying out information exchange and other cooperation with France, Australia, Indonesia, and other nations.

The following are examples of multinational cooperation in life science.

The OECD Scientific and Technological Policy Committee is examining how to internationally balance the measures for securing the safety of and regulating biotechnology.

Examination of the philosophy on joint research and technical training for developing nations is underway under international cooperation agreed upon at the summit.

What is described heretofore is a general view of the agency's policies for promoting life science.

The Life Science Planning Room established for this promotion was renamed the Life Science Planning Department on 1 July 1984. According to the forecast for the future of science and technology ranging to the 21st century, life science will play a leading role in their promotion. The agency is planning to promote it further, cooperating with the other authorities concerned.

MHW's Life Science

Tokyo PUROMETEUSU in Japanese Jul-Aug 85 pp 27-29

[Article by Soichiro Iwao of the Life Science Office, Health and Welfare Ministry Secretariat General Affairs Section: "Aiming Towards Elucidating Cancer Instinct"]

[Text] Life science elucidates life phenomena, applies biological technologies, and regards life ethics for human livelihood, life, and survival. It is not an overstatement to say that all health, medical, and welfare administration policies are connected with life science. Hereunder, discussion will be made as to the Ministry of Health and Welfare's connection with life science, mainly referring to the matters within the jurisdiction of the Life Science Room established in the minister's Secretariat General Affairs Department in fiscal 1983.

Life Science Room

Engaged in the collective coordination of MHW's scientific and technological policies, as well as the formulation and coordination of the policies regarding technology related to DNA. They have hitherto been carried out by individual competent bureaus without close horizontal cooperation and without the ministry's all-out effort. The room is expected to contribute to establishment of the ideology of the policies for welfare science and technology and to the forecast for historical transition. In particular, the progress of biotechnology is expected to promise the striking development of the application of hightech science and technology to health and medical purposes.

Medical Measures Related to Biotechnology

With the progress of cellular and genetic research, the causes and crisis mechanism of various diseases are being increasingly explicated.

(1) Infectious diseases

The detail and accurate analysis of the pathogens of influenza, Japanese encephalitis, and other diseases has become possible by using monoclonal antibodies. The analysis of pathogen genes and proteins has played an important role in preventing disease infection by elucidating its routes and proliferation mechanism. Vaccines are used to prevent infectious diseases. They weaken the toxicity of viruses and other pathogens or inactivate them. The difficulty of securing their materials and their safety has posed various problems. Those containing antigenic but nonpathogenic proteins have been developed by using recombinant DNA technology. For example, the recombinant HB vaccine for B-type hepatitis has already undergone clinical testing.

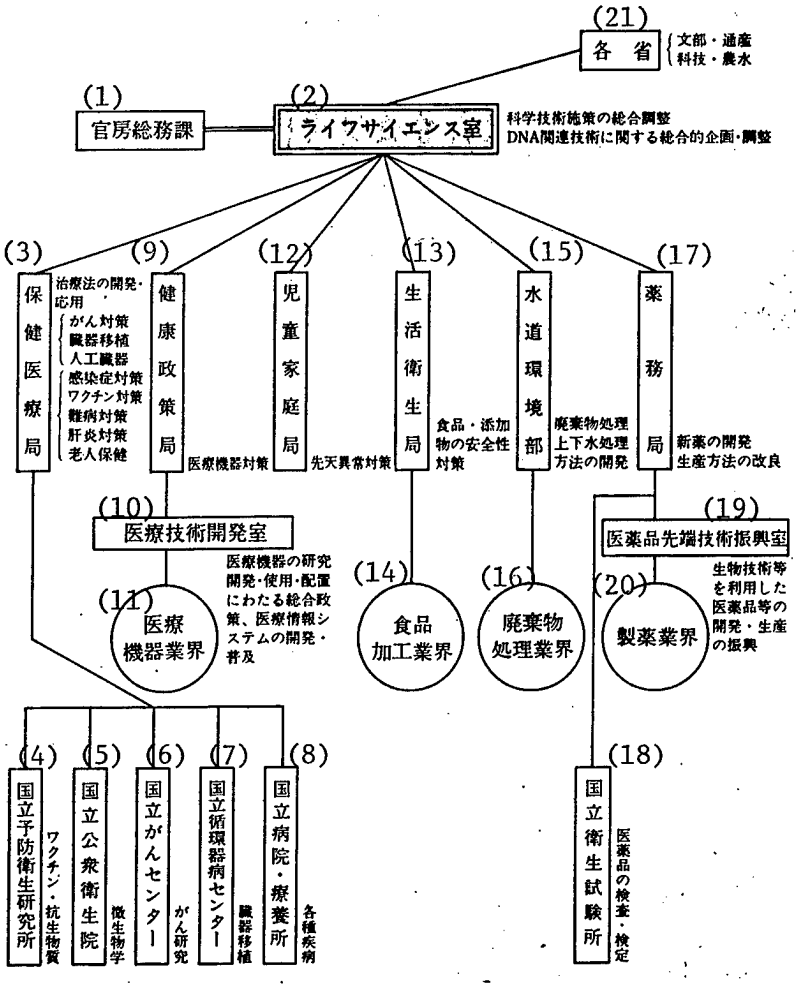

Figure 1. MHW's Organizations Related to Hightech

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[Key to Figure 1]

1. Secretariat General Affairs Department
2. Life Science Room (Collective coordination of science and technology policies, collective planning, and coordination of technology related to DNA)
3. Insurance and Medical Treatment Bureau (development and application of therapeutic methods; countermeasures to cancer, organ transplantation, artificial organs; countermeasures to infectious diseases, vaccines, countermeasures to intractable diseases, countermeasures to hepatitis, health of the aged)
4. National Institute of Health (vaccines, antibiotics)
5. Institute of Public Health (microbiology)
6. National Cancer Center (cancer research)
7. National Institute of Circulatory Organ Diseases (organ transplantation)
8. National hospitals and sanatoria (various diseases)
9. Health Policy Bureau (Measures for medical apparatuses)
10. Medical Treatment Technology Development Room (Formulation of collective policies regarding the study, development, use and layout of medical apparatuses; development and diffusion of medical information systems)
11. Medical Apparatus Industry
12. Children and Families Bureau (Countermeasures to congenital abnormalities)
13. Life Health Bureau (Measures for the safety of foods and food additives)
14. Food processing industry
15. Water Supply Environment Division (Development of methods for treating wastes, service water, and sewer)
16. Waste treatment industry
17. Pharmaceutical and Supply Bureau (Development of new medicines, improvement of production processes)
18. National Institute of Hygienic Sciences (Examination and verification of medicines)
19. Pharmaceutical Hightech Promotion Room (Promotion of the development and production of medicines, etc., by applying biotechnology)
20. Pharmaceutical industry
21. Various ministries (Master of Education, MITI, Science and Technology Agency, MAFF)

(2) Congenital metabolic abnormalities

A gene recombination technique has been developed for treating enzyme aporinosis and hemoglobin abnormal disease. Its test-tube experiment has just started. It is necessary for securing its safety and accuracy as well as its ethical assurance to continue basic research sufficiently.

(3) Immunity abnormality

The genetic basis of immunity control mechanism is elucidated so the abnormal arrangement of genes has become clear respecting actual diseases. If production of monoclonal antibodies to materials in vivo becomes possible, highly specific diagnostic medicines and examination reagents are expected to become obtainable. As to therapy, a specific immunity control method is expected to be useful for organ transplantation. It is intended to produce monoclonal lymphocyte antibodies with high transplanted antigen killer activity in great quantities for controlling immune response by cell fusion.

10-Year Comprehensive Strategy Against Cancer

Cancer ranks first among the causes of death in Japan. In particular, death due to cancer of those in the prime of life exerts a great influence on both society and households since they assume an important position there. Cancer research is busily underway at the National Cancer Center as well as at national hospitals and college research institutes. "The 10-Year Comprehensive Strategy Against Cancer" framed by the government is intended to promote a stress-placed, concentrated, and multi-angle approach to the elucidation of the cause of cancer within 10 years. In fiscal 1985, research is divided in six categories: 1) human carcinogenic genes; 2) human carcinogenesis due to viruses; 3) its promotion and suppression; 4) developing early diagnostic technology; 5) developing therapeutic methods based on new theories; and 6) immunity control mechanisms and materials. Included therein are "indexing and identifying new cancer genes," "production of monoclonal antibody for human cancer and its application to diagnosis," "the crisis, therapy, and prevention of human cancer due to DNA cancer viruses," and many other biotechnology-applied research subjects. Biotechnology covers the method for the early discovery of cancer by using a tumor marker and the TNF therapeutic method for efficiently killing only its cells.

Late in September 1984, the Cancer Research Promotion Foundation as well as the National Institute of Health and the National Institute of Hygienic Sciences jointly established an institution named "the Research Resource Bank" under the cooperation of the center, colleges, and research institutes to constantly supply the information indispensable for rapidly progressing biotechnology as well as cells, genes, and other research materials under the project based on the strategy. The hygienic science institute is engaged in cancer cell banking for preservation, supply, and quality control, and the health institute in cancer gene banking.

Living Environment and Biotechnology

(1) Treatment of service water and sewer

The malodor of pipe water becomes problematic with the increase of contamination of water sources. Used to solve this problem is a biotechnology-applied technique called bio-oxidation treating method in which bacterium- or diatom-attached biomembranes are adopted to decompose contaminant materials. Good tasting, safe water can be secured thereby. As to sewage treatment, research is underway for searching for and improving the microbes useful for making undecomposable materials harmless and for upgrading their treatment.

(2) Treatment of wastes

At present, it is necessary to develop technology for the optimum treatment of wastes. It is also an important task in saving resources and energies to effectively use wastes. Anticipated in this connection is the use of biotechnology, e.g., development of techniques for gas recovery by methane fermentation, aerobic reclamation for stabilizing soil, biological denitrification and dephosphorization in the treatment of eutrophic and other sewers, and liquid fertilization of night soil.

Biotechnology and other high technology contribute much to the health and medical sectors. Life science will become increasingly significant for the scientific forecast of man's future and for his coexistence and coprosperity. The ministry intends to promote research and development for improving high technology as well as other sectors of technology.

MITI Research, Development

Tokyo PUROMETEUSU in Japanese Jul-Aug 85 pp 29-31

[Article by Shuichi Oka; Office of Next Generation Industrial Technology, MITI's Industrial Technology Institute: "Research Development of Next-Generation Industries Basic Technologies"]

[Text] Biotechnology has progressed rapidly since its application to industry attracted the attention of those concerned. Bio-industry based on it is expected to develop in the future. The Ministry of International Trade and Industry is carrying out comprehensive policies for its promotion. Included among them is "New-Generation Industry Basic Technology Research and Development System" for promoting technological development. Described hereunder will be the summary of the system and the subjects of the research and development being carried out under it.

Summary of New-Generation Industry Basic Research and Development System

The following standards have been set up for the research to be carried out on the basic technology indispensable for establishing new-generation industries under this system, founded in fiscal 1981.

(1) High innovation and wide, far-reaching influence;

(2) Considerable risk--about a 10-year period as well as a large amount of funding is necessary for research and development;

(3) Development should be initiated early because research has already started in the United States and Europe.

Research is now underway on 12 subjects (total of 13 because 1 subject is added in fiscal 1985) selected accordingly in 3 sectors--new materials, biotechnology, and new functional elements--by 81 corporations, 28 national laboratories and research institutes, and 25 college theaters.

Under the system, a majority of the research and development is carried out in parallel to increase their efficiency and the 10-year period is divided into thirds. For each division of the 10-year period, targets are fixed and the evaluation committee consisting of specialists evaluates the progress and results of development accordingly.

Biotechnology covers three subjects: 1) bioreactors, 2) cell mass-culture technology, and 3) recombinant DNA application technology. For all of them, research on the second stage is now underway with evaluation on the first stage already completed.

The following is the summary of the results of the first-term research and development. In bioreactor technology, bacteria with high material production powers and high obstruction resistances have been developed by breeding their many useful stocks screened out of soil. As to cell mass-culture technology, high-density culture is carried out by using no-serum media. Success has been attained in the selection, breeding and long-period generation-succeeding culture of useful physiology-activating material producing stocks. With respect to recombinant DNA technology, different kinds of target genes have been successfully manifested in colon and hay bacillus and enzyme hosts by establishing the vectors. In connection with these results, 149 patent applications had been submitted and 86 papers had been submitted at domestic and overseas academic meetings as of March 1985.

The first-term basic research has proceeded as described heretofore. In and after the second term, nevertheless, it is necessary for achieving success in applying the technology to industries to solve a number of problems and make further effort in research and development.

The progress and situation of research and development will be described hereunder in connection with each of the subjects.

Bioreactors

In-vivo reaction catalyzed by microbes and enzymes progresses with specific efficiencies under moderate conditions. The development of bioreactors by utilizing this function in vivo leads to that of the resource- and energy-saving type chemical processes to be substituted for high-temperature,

high-pressure, energy consuming type ones. The following is underway to develop bioreactors to be substituted for energy consuming ones (oxidation, synthesization, etc.) of the main reactions in the chemical industry for considerably saving resources and energies:

1) Research for fixing materials and methods;

2) Research for improving the functions of enzymes;

3) Research on co-enzyme reproduction system-fixing reduction bioreactors;

4) Research on bioreactors to be substituted for oxidation processes.

Cell Mass-Culture Technology

Animal cells produce various, useful physiology-activating materials; it is an important task to develop technology for their economic production. It is indispensable for this purpose to establish this for the economic and constant mass-culture of animal cells. The following is underway for developing substitutes for unborn cattle serum that is indispensable for culturing animal cells and the basic technology for their high-density culture.

1) Basic research on the factors in controlling the proliferation of cells;

2) Research on the processes for producing industrial materials by no-serum culture medium, culture engineering, and other optimum culture methods;

3) Research on the processes for producing industrial materials mainly by developing high-density cell culture and no-serum culture medium methods;

4) Research on the processes for producing industrial materials by using suspended cells;

5) Research on the processes for producing industrial materials by using cells of marrow origin;

6) Research on the processes of producing industrial materials by using cells of epithelium origin.

Recombinant DNA Application Technology

It is important among the subjects of biotechnology to recombine DNA pieces of different living bodies, transfer recombinant ones to hosts, and proliferate them to obtain the products of different sorts of genes. This ensures the development of industrially-applicable microbes and functions peculiar to the respective sorts of living bodies. The following is carried out to develop microbes with industrially-applicable, high-efficiency material production functions by using existing host-vector systems and those to be developed for saving resources and energies for chemical industry.

1) Research on basic, recombinant DNA technology;

2) Research on developing bacterium stocks for high-oxidation reactive processes;

3) Research on methods for developing high-efficiency secretion stocks of hay bacillus system;

4) Research on methods for developing stocks of high-secretion enzyme system.

New-Generation Basic Industrial Technology Research and Development System

Subject	R&D project (fiscal year)	Nongovernment conductor	National laboratory research institute
Bioreactor	1st term 81–85; 2d 85–88; 3d 88–90	Biotechnology Development Research Association	Fermentation Research Institute; Research Institute for Polytechnics and Textiles; National Chemical Laboratory for Industry
Cell mass-culture	1st 81–84; 2d 84–87; 3d 87–89	" "	Fermentation Research Institute
Recombinant DNA	1st 81–85; 2d 85–89; 3d 89–90	" "	Fermentation Research Institute; Research Institute for Polytechnics and Textiles; National Chemical Laboratory for Industry

Agriculture, Forestry, Fisheries Ministry

Tokyo PUROMETEUSU in Japanese Jul-Aug 85 pp 31-33

[Article by Teruo Yamamoto, Office of Biotechnology, MAFF Agriculture, Forestry and Fisheries Technical Council Office: "Development of New Species, New Food Products, and the Gene Bank"]

[Text] The Ministry of Agriculture, Forestry and Fisheries is making an all-out effort in research and development in biotechnology, considering it of key significance for strikingly increasing the productivity of agriculture, forestry, food, and other related industries.

In this direction the ministry has established national laboratories and research institutes, including the Institute of Agricultural Organism Resources (December 1983), a biotechnology development promotion system, including the Biotechnology Room (April 1984), and considerably increased related budgets. Its development is underway under close cooperation between government authorities as well as industrial and academic circles under

long-range projects. Its summary will be described hereunder in connection with its 1985 budget (see the attached table).

Establishment of Developmental Promotion System Under the Cooperation of Administrative, Industrial and Academic Circles

The ministry holds promotion conferences consisting of leading figures in administrative, industrial, and academic circles for deliberation on and examination of the basic direction of promoting development, invites researchers to national laboratories and research institutes, and promotes research on "breeding" jointly with nongovernmental research institutes.

Strengthening National Institutes' Leading and Basic Research

The ministry has decided that national laboratories and research institutes should play a leading role in promoting basic and other research and development for rapidly progressing biotechnology. In this direction the following subjects have been selected.

(1) Development of organism resources by cell fusion and nucleus transplantation

Development of technology of fusion and nucleus transplantation between different cells to produce new ones, mass-production of monoclonal antibodies and other useful materials, and copying of excellent livestock systems that are not possible with conventional cross-fertilization and mutation methods.

(2) Elucidation of gene-manifesting mechanisms in agricultural organisms

Making of DNA libraries of the genes of main agricultural produce and microbes, analysis of the structure of useful genes, development of introducing them into cells, and elucidation of the mechanism of manifesting the character of incorporated genes on the stage of cells.

(3) Elucidation of physiological and hereditary mechanisms of photosynthesis and respiratory functions

Elucidation of physiological and hereditary mechanisms of C_3- and C_4-type plants for their striking increase in photosynthetic capacity

(4) Development of technology for applying microbes and enzymes to biomass conversion

Search, improvement, mass-production and fixing of microbes and enzymes for efficiently converting biomass resources into foods

(5) Development of technology for breeding by gynogenesis of fish and shellfish

Generation of female fishes advantageous for producing large-sized individuals that generally grow rapidly.

MAFF's Biotechnology Budget (Unit: Y10 billion)

Items	Fiscal 1984	Fiscal 1985
I. Establishment of the system for collectively promoting biotechnological development under close cooperation among administrative, industrial, and academic circles	(14)	(13)
II. Promotion of national institution leading and basic study and development of biotechnology	(687)	(761)
1. Development of new organism resources by cell fusion and nucleus transplantation (FY 1982-1986)	228	227
2. Elucidation of gene manifestation mechanism in agricultural organisms (FY 1984-1988)	122	133
3. Elucidation of the physiological and genetic mechanism of photosynthesis and respiratory functions (FY 1978-1982)	113	111
4. Development of new technology for applying microbes and enzymes to biomass conversion (FY 1982-1990)	50	55
5. Technological development of breeding by gynogenesis of fish and shellfish (FY 1985-1989)	0	28
6. Research on long-period preservation	75	107
7. Research for bio-hightech seed culture	100	100
III. Promotion of development of biotechnology by the best use of nongovernmental resources	(395)	(457)
1. Food industry development of bioreactor systems (FY 1984-1989)	206	244
2. Development of cell culture and other common basic technology for developing new agricultural chemicals (FY 1984-1988)	45	66
3. Development of technology for improving microbe and plant cells by fusion (FY 1984-1988)	49	48
4. Development of simple methods for immunologic diagnosis of livestock diseases (FY 1984-1988)	45	45

[continued]

[MAFF's Biotechnology Budget--continued]

Items	Fiscal 1984	Fiscal 1985
5. Development of technology for efficiently producing seeds and seedlings by tissue culture (FY 1983-1987)	50	55
IV. Improvement of the collection and management of genetic resources and information	(182)	(729)
----Agricultural, forestry and fishery gene banks----		
1. Establishment of system for collective management and utilization of genetic resources of agricultural, forestry and fishery organisms and genetic and breeding information	182	390
2. Establishment of facilities for managing genetic resources of agricultural, forestry and fishery organisms	0	338
Totals	1,278	1,960

(6) Research on long-period preservation of microbes

Development of long-period stable preservation of important microbes, and the elucidation of hereditary characters for breeding components

(7) Research on culturing bio-hightech seeds

Commission mainly to colleges of basic, interdisciplinary research with a great potential of leading the culture of seeds significant for the development of biotechnology

Promotion of the Development of Biotechnology by Active Use of Nongovernment Resources

Joint research is underway for application and practical use of biotechnology in nongovernment sectors that have great potential and require early innovation. The following are the sectors as well as their technological development tasks.

(1) Development of bioreactor systems in the food industry

Incorporation of biosensors by applying fixed enzymes and microbes to the production of carbohydrates, proteins, organic acids, and fats

(2) Development of common-basis technology of cell culture for developing agricultural chemicals

Cell mass-culture and fusion, and DNA recombination for developing agricultural chemicals of the materials of microbe, and animal and plant cell origin

(3) Development of technology for improving by fusing microbe and plant cells

Establishment of technology of the protoplast and fusion of cells and the efficient selection and culture of hybrid cells for early practical use for microbe and plant cells according to purposes

(4) Development of simplified methods for diagnosing livestock diseases by using immunity

Technology of mass producing and purifying virus antigens and monoclonal antibodies for promoting practical application of enzyme immunity measuring methods and the diagnostic systems to which they apply

(5) Development of technology for efficiently producing seeds and seedlings by tissue culture

Production and efficient breeding of excellent individuals and mass proliferation of seeds and seedlings for the practical use of tissue culture technology

Establishment of Agricultural and Fishery Gene Bank

It is necessary for the dramatic growth of biotechnology to collect various kinds of genetic resources to be applied to it. For this purpose a system is being established to collectively utilize information of hereditary resources and breeding of plant, microbe, animal, fish, and other agricultural and fishery organisms in and after fiscal 1985.

The ministry is planning to efficiently push forward biotechnological research and development to acquire their fruits in the next century.

Education Ministry

Tokyo PUROMETEUSU in Japanese Jul-Aug 85 pp 33-34

[Article by Kazufumi Yoshida, Research Support Division of the Ministry of Education's Bureau of Internal Science: "Basic Research Focusing on DNA Recombination"]

[Text] Measures for Promoting Bioscientific Research

Life science is intended to elucidate the substance of life phenomena by physical, chemical, engineering, and other methods beyond the conventional

scope of biology, medicine, and agriculture. In particular, it is rapidly progressing due to the latest development of molecular biology and genetics as well as the technology of handling genes for DNA recombination and cell fusion.

The progress of the study and application of life science is anticipated since it rapidly elucidates life phenomena and contributes much to the settlement of medical, food, and environmental issues.

College and other research institutes are attaining important results in a wide range of basic through hightech research in life science. The Ministry of Education has increased the subsidies for scientific research to promote it at national colleges, where the promotion of particularly basic research is significant for its furtherance in parallel with the recent rapid progress of life science. The Bioscience Department established in April 1983 in the Specific Research Promotion Division of the Academic Commission is now examining measures for promoting life science research and education.

Current Status on Research

In life science, a wide range of basic through hightech research and education is underway at medical, scientific, agricultural, and other departments concerned; at Tokyo University Medical and Scientific Research Institute, Tohoku University Acid Fast Bacterium Diseases Research Institute and other research institutes attached to colleges; Osaka University Cellular Engineering Center and other education and research facilities; and many other research institutes and facilities.

By 1984 the ministry had established 7 gene-analyzing laboratories in cooperation with 67 colleges. Since 1980 Tokyo University Medical and Scientific Research Institute for bioscientific research on recombinant DNA and genes had handled the education and training of researchers and students and the safety control of recombinant DNA experiments. With fiscal 1985's budget it is planning to set up Hokkaido University Genetic Experiment facilities and two for two colleges (one facility for one university; that attached to the Scientific Department will be reorganized into that for the use in common to university).

Among national college common-use institutions for joint research by teachers and others, the National Institute of Genetics as well as the Basic Biology Institute and the Physiological Institute of Okazaki National Joint Research Institution is involved in life science.

The genetic research institute was established by reorganizing the institution within the ministry's jurisdiction into a national college common-use one in April 1984 to encourage cooperation with the researchers concerned in other related sectors. The 13 sections of its 5 molecular genetics research systems are engaged in collective study.

The basic biology institute was set up in May 1977. The 13 sections of its 3 cellular biology research systems are occupied in collective research to elucidate basic life phenomena.

The physiological institute was set up in 1977 also. The 13 sections of its 4 molecular physiology research systems are employed with collective research to elucidate human body life acitivites.

Increased Scientific Research Subsidies

Scientific research subsidies are intended to contribute to the progress of excellent academic study. They are being increased for future basic and forerunning research. Five bioscientific sectors, including "Nucleic Acid Confirmation and Discrimination" have been added in fiscal 1985 to "specific research" sectors to be subsidized to promote basic study.

Promotion of Recombinant DNA Experimentation and Maintaining Safety

In the recombinant DNA experimentation indispensable for bioscientific research, recombinant molecules are obtained by transplanting cell DNA (gene body) and other types of DNA by using enzymes in test tubes and transplanting it in living cells to proliferate. This method is very significant for the analysis of DNA, is useful for life phenomena, and is highly applicable for producing medicines and breeding farm produce since it can be directly handled. The technology is expected to contribute much to the promotion of bioscientific research. Its safety, however, should be sufficiently noted since there still remain unknown phenomena. For this purpose the United States, France, West Germany, and Britain have each formulated recombinant DNA experiment guidelines.

In Japan it is necessary for promoting bioscientific research to carry out recombinant DNA experimentation early and appropriately. It has already started at college and other research institutions following the ministry's Notification No 42/1979, dated 31 March 1979, of "College and Other Research Institutions' Recombinant DNA Experiment Guidelines" on the basis of the Academic Commission's representation.

The United States and other nations have revised experimental guidelines to optimize regulation regarding safety on the basis of knowledge obtained in the course of research on DNA recombinant experiments.

In Japan the ministry issued Notification No 131/1982 on 31 August 1982, a total revision of the experimental guideline, to optimize research on the basis of the Academic Commission's representations in "On the Revision of the Guideline for Recombinant DNA Experiments at Research Institutions of Colleges, Etc." in July 1982. Due consideration is given therein to the safety of research on the basis of the guideline at present. As of March 1985, recombinant DNA experiments are underway at the research institutes of 105 colleges. In fiscal 1984, it amounted to about 2,100 cases.

Promotion of Cancer Research

The suppression of cancer is an earnest, worldwide wish. The colleges with a wide range of experience in cancer research are expected to play a very significant role therein. The ministry has endeavored to promote it with

various measures; for example, the addition of "special cancer research" to the objects of scientific research subsidies.

The government also issued its "10-Year Collective Strategy Against Cancer" at a meeting of the ministers concerned to collectively and efficiently promote cancer research. Under this decision the authorities concerned cooperate with each other for its promotion.

The strategy is intended to elucidate the cause of cancer on the basis of a variety of results of research and reflect the results of this elucidation in its prevention, diagnosis and treatment within 10 years.

The ministry is planning to make an all-out effort in achieving strategic targets and to cooperate with other authorities concerned.

Overview of Various Companies

Tokyo PUROMETEUSU in Japanese Jul-Aug 85 pp 36-45

[Article by editorial department: "Probing the Current Situation of Life Science in the Industrial Circle"]

[Text] Japan's life science research started after the Science and Technology Council's Report No 5 was issued in 1971, citing life science as among the new scientific and technological research sectors on which the government should place importance. In recent years the development of basic biotechnology research has progressed rapidly, e.g., the research on recombinant DNA application, cell mass-culture, and bioreactors has started, in addition to that on aging control, artificial organs, intelligent machinery, and organism-activating materials.

Listed below are the answers of corporations involved to the editor's five questions on the present and future of research and development.

Items in Questions

(1) Process of research, development, and commercializing

(2) Research and development systems

(3) Summary of research projects

(4) Present problems and issues

(5) Plans and prospects for industrialization

Kao Corporation Research and Development Center

(1) We are developing life science on the basis of our conventional know-how and experience for the upgrading and combination of technologies. The targets of this development include those of oil and fat chemical technology,

development of microbe and enzyme application technology, search for physiology-activating materials for human body dermatology, and plant breeding technology for increasing oil and fat resources.

(2) A biological science section (five research rooms) established in the Tochigi Research Institute and the bioengineering research groups organized in the Kashima Research Institute and Production Technology Research Institute are engaged in basic study and the study for commercializing the results of basic research sections respectively under the supervision of the Research and Development Center.

(3) Development of bioreactors for producing useful aliphatic family derivatives (MITI New-Generation Industry Basic Technology Research and Development Project) and development of the technology for hydrolyzing oils and fats by enzyme methods (MITI Industrial Activation Research and Development System). Oil and fat resources: Tochigi Research Institute and our farms in the Philippines and Mindanao are cooperating in developing the technology for breeding and culturing palms.

(4) It is most significant for life science to promote basic research since it has not yet firmly been established.

(5) In industrialization, priority is given to the subjects now in the course of development. Its results would therefore provide future prospects.

(Tsukasa Kawada)

Calpis Food Industry Company--Research and Development Center Planning Room

(1) We started the study and development of life science on the basis of past joint research on lactic acid fermentation with the Institute of Physical and Chemical Research for scientifically elucidating the health maintenance effect of "acidic milk," the material of Calpis.

The research has evidenced the life elongation effect of acidic milk, as well as its favorable effects on flora in the intestines, activation of the renal function, and increase of the immunological function. Research on the immunological function has involved the development of diagnostic medicines by utilizing immunological reaction.

(2) Life science: the subgroups of 15 research staff members mainly from the Sagami Branch Room (completed in July 1982) of the research and development center are engaged in research under the direct supervision of a manager.

Emphasis is placed on the acquisition of know-how at outside research institutions, joint research with them, and efficient applied research.

(3) Health maintenance effect of acidic milk:

--search for and utilization of the useful bacteria in the intestines;

--relation between acidic milk and blood pressure, etc.

Development of diagnosing medicines:

--development of acute leukemia diagnosing medicine by using monoclonal antibodies;

--development of various kinds of diagnosing medicine by using immunological reaction.

(4) 1. Health maintenance effect of acidic milk: back data will be accumulated further for developing health and medical foods.

2. Development of diagnostic medicines: field test measurement is being rechecked at present.

(5) Research is underway for developing some kinds of diagnostic medicines by using the above technology in fiscal 1986.

(Norio Suzuki, manager)

The Chemo-Sero Therapeutic Research Institute--Research and Development Division

(1) Since its founding, this institute has been engaged in microbiology and immunology. The emphasis of research and development has been placed on the immunological prevention and immunotherapy of diseases. Their results include the development of vaccines for human bodies and animals, blood-plasma sectioning drugs, and clinical reagents. Key importance is attached to independent research. For several years, emphasis has been kept on the development of new-generation biological drugs by introducing genetic and cellular engineering technology.

(2) The Research and Development Division organizes research on subjects selected by the New Line Development Committee. Teams are organized for each research sector and project teams for important subjects. Production sections are independently engaged in development and for some subjects carry out research under the joint projects with the division. Joint development is also underway with colleges as well as other domestic and overseas cooperation.

(3) Research and development sections put primary importance on gene-handling projects. Research is underway for the production of human and animal virus antigen proteins by mass-culture hosts. Technology is being developed for producing B-type hepatitis vaccines under the Research Development Corporation of Japan's commission. In the cell handling project, a total of 12 teams are engaged in developing technology for the mass

production and practical application of monoclonal antibodies and research on synthetic peptide and animal infections.

(4) Important tasks include increasing the efficiency of research and development, increasing information acquiring and cost competition capacity, increasing overseas orientation, and securing research personnel.

It is necessary to increase the capacity of technological development for switchover to recombinant and synthetic-peptide vaccines and upgrade purification and production technology for developing physiology-activating materials.

(5) This fiscal year the Kikuchi Research Institute will begin operation. All research and development sections will be collected in it and the organizations concerned will be reintegrated for increasing the efficiency of research and development.

An enzyme recombination B-type hepatitis vaccine is in the experimental stage. Application will be made for its production in the next fiscal year. At the same time, we are planning to complete a production plant system for its mass-production. This project is expected to contribute to the increased capacity of the development and cost competition of recombinant technology applied drugs.

(Sadao Susumu, manager)

Kyowa Hakko Kogyo Company--Biological Research Institute

(1) History

1947: Production of penicillin started.

1951: Streptomycin production technology from Merck Co. introduced.

1956: Process for producing glutamic acid by fermentation method invented.

1959: Licensed to produce mitomycin.

We started initiating life science immediately after World War II. The emphasis of research was placed on amino acids, proteins, peptides, enzymes, and other basic materials of life.

Full-scale inroads into new biotechnology were made as late as 1981. Its practical use, however, has been made at a fast tempo; for example, the nobacillus proliferation of lily suckers started in 1982 and the B-interferon and biomass-alcohol pilot plants set in operation in 1983 and 1984, respectively.

1. Technology to be commercialized in the near future.

--Fixed enzymes, fixed bacilli, and biomass alcohol

2. Application of recombinant DNA methods

--Physiology-activating peptide-interferon, (interoykin), prolactin, TNF, etc.

--Application to process improvement

--Protein engineering

3. Mass-culture and fusion of animal and plant cells

(2) Tokyo Research Institute (Central Research Institute):

Development of microbe recombination DNA methods, protein engineering, mass-culture of animal cells, monoclonal antibodies

Technical Research Institute:

Fixed bacilli, application of cell fusion and recombinant DNA methods to process improvement

Biological Research Institute:

Mass-culture of plant cells and organs, cellular engineering

(3) Medicines:

Physiology-activating peptide, antibiotics, monoclonal antibodies, production of physiology-activating materials by animal and plant cells

Production of materials other than medicines:

Fermentation of amino acids, development of clinical enzyme drugs

Others:

Research on cogogenes, cellulose saccharification by microbes, and methods for quickly mass-proliferating merriclonal bacilli

(4) Shortage of researchers and imbalance of distribution:

Particularly problematic is the shortage of the absolute population of recombinant DNA, its analysis, and cell fusion experts, as well as the excessive posting of the small population of experts in microbe sections.

Future tasks: eucaryota cell engineering, particularly full-scale research on food issues

At present "what" has become more significant than "how" in research. It is important to define this significance in consideration of its worldwide trend.

(5) Switchover from recombinant DNA to protein engineering

Research will be switched over from pronuclear microbes to enzymes and animal cells to plant cells.

Some physiology-activating materials will be commercialized in the near future.

Plant cell engineering has progressed rapidly since last year to provide new business chances.

(Masachika Kawaai, manager)

Kirin Brewery Company--Research and Development Department

(1) Long-range operation projects

Promotion of research and development in life science (medicines, seeds, seedlings) and development of business lines based on their results

Promotion of the study and development of new-generation technology for beer and other business lines, and establishment of leading company's basis

Early commercializing by investment in other companies' capital and technical ventures with them.

(2) Head Office Research and Development Division and Material Division coordinate the promotion of research and development. The research on medicines and enzymes is underway by the Development Science Research Institute and that on new-generation beer technology by the Beer Science Research Institute.

Cooperation will be received from bioventures (Amgen, Plant Genetics, etc.).

(3) Development of technology for recombining the genes of erythropoietin (blood hormone) (its particulars cannot be revealed as yet)

Development of new-generation brewery technology and practical use of artificial seeds by using bioreactors.

(4) We are required to further increase combined competitive capacity although the technology in some specific sectors has considerably advanced.

Tasks: increase in the basic capacity of research and development and combination of research and development capacities.

(5) The projects and tasks now underway will be accomplished one by one.

The research now underway will be carried on, without their sudden extension, until attaining practical use.

(Keiichi Morimoto, assistant manager)

Suntory--Pharmaceutical Planning Department

(1) Based on the inroads in the pharmaceutical industry in 1979, Suntory established the Biological and Medical Research Institute in November of that year. Putting emphasis on biotechnology that was established then, Suntory succeeded in the mass production of physiology-activating peptide as well as the development of diagnostic medicines by using monoclonal antibodies and "cancer missile therapy" by using their combinations with toxins.

(2) Biotechnology groups have been organized in the institute in addition to pharmaceutical ones. The institute has genetic engineering, molecular biology, cellular engineering, immune engineering, biological engineering, and biological pharmaceutics research rooms. They are engaged in the culture of animal cells, the isolation of bipeptides and the fixing of their structure; the separation and cloning of m-RNA; the development of high-manifestation vectors; the culture, purification, and scaling-up of recombinants; and the acquisition, use, and assay of biological drugs and monoclonal antibodies.

(3) A project is being carried out to produce gene-recombinant interferon-gamma by using colon bacillus. Under this project research is also underway with (Shaling Plaw) of the United States. The American company has been licensed to produce the bacilli developed by Suntory.

The research on gene-recombinant TNF is being carried out jointly with (Biogene). Research on "cancer missile therapy" for applying monoclonal antibodies to cancer and more than 10 other projects are also underway.

(4) We consider the following. Japan is included among the vanguard of nations in cloning technology using recombinant DNA methods, the improvement of plasmid, synthesization of genes, and the culture of recombinants, but behind other advanced nations in cellular biology for culturing cells and the collection of bacillus stocks for supporting them. It is necessary to emphasize the development of produce purification technology. Unique things are difficult to develop because Japan is rather weak in basic technology.

(5) We intend to accomplish the projects now underway by completing clinical research, develop antipernicious tumor medicines such as interferon-gamma and TNF, and draw out a plan for constructing a plant for their early commercialization.

(Takashi Hirabayashi, assistant manager)

Sumitomo Chemical Company

(1) Life science is divided into three sectors:

1. Agriculture and foods
2. Pharmaceuticals and health
3. Other chemical industries

We have several decades of history of their research, development, production, and sale.

(2) About 1,700 employees, one-fourth of the total, are attached to research sections that are divided among the 8 research institutes under the supervision of a director in charge. The researchers in life science account for about one-third of them, except those in pharmaceutical sections (Sumitomo Pharmaceuticals).

(3) 1. Agriculture and foods

Control of growth environments (irrigation systems, films, culture soils, etc.), management of culture (coat seeds, fluid seeding, etc.), protection of plants (chemical and biological agricultural medicines), breeding, extraction and utilization of natural things

2. Medicine and health

Synthetic medicines, biomedicines, examination and diagnostic medicines, biomaterials, etc.

3. Chemical industry

Energy-saving chemical processes, optical metamer separation, etc.

(4) 1. It is difficult for corporations to cover a wide range of basic research. Therefore, cooperation between them, with their uniqueness maintained, is necessary.

2. As overseas competition is becoming heated, it is desirable that non-government corporations use cellular and genetic banks as well as data bases.

(5) We are planning to continuously emphasize research, development, and commercialization, and increase business lines by adding new technological sectors to fertilizers, agricultural chemicals, agricultural materials, and medicines in which we have a long history.

(Yoshihiko Nishizawa, managing director)

Takeda Chemical Industries--Central Research Institute Biological Engineering Laboratory

We are carrying out research and development for developing new lines in order to contribute to the progress of pharmaceuticals and health. All of their subjects are therefore included in life science. Its answer is concerned in biotechnology in a rather narrow sense.

(1) 1971: Microbe containment facilities established.
February 1981: Agreement for joint development of rIFN-α with Hoffmann La Roche concluded.
June 1981: Biological Engineering Research Institute established, full-scale research on biotechnology started.
January 1982: Clnical test of rIFN-α started.
August 1982: P_3-level mass production equipment installed.
March 1984: Clinical test of rIFN-γ started.
June 1984: Clinical test of rIFN-2 started.
February 1985: Application for approval of production of rIFN-α.

(2) Central Research Institute (about 1,100 employees) plays a major role in the study and development of new pharmaceutical lines. It has eight institutes for chemical, fermentation produce, biological, biological engineering, pharmaceutical, medicine production, crude drug, and medicine safety research, as well as the Production Technology Research Institute and four division institutes for food, agricultural medicine, stock raising, and chemical research. Research and development on biotechnology is undertaken mainly by the biological institute (about a 70-member staff) and those on its downstream side by the fermentation produce institute.

(3) 1. Production of the physiology-activating proteins of human origin (IFN-rIL-2, B-type hepatitis vaccine, etc.) by recombinant DNA methods

2. Production of human antibodies by mouse-human-human hybridoma (subject under MITI's New-Generation Project)

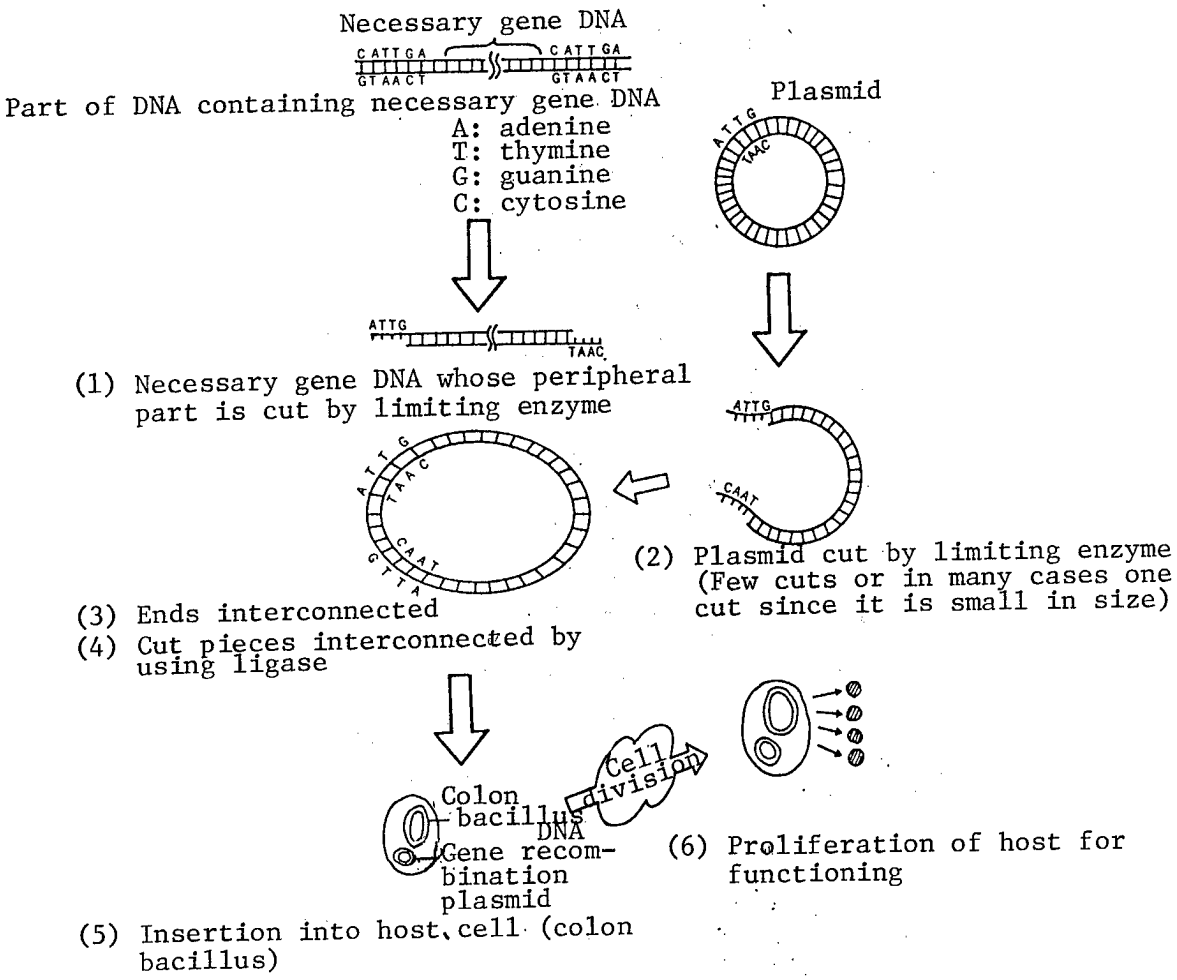
3. Improvement of methods for microbe secondary metabolism production by applying recombinant DNA

4. Tissue culture of plants and their breeding.

(4) In biotechnology there still remains a variety of problems to be solved in the future. In the sector of recombinant DNA, for example, proteins with a complicated structure are not so easy to produce. Even colon bacillus, whose study is most advanced, has not gone further than storing simple proteins with a comparatively small molecular weight. It is therefore a pressing need to improve gene manifestation systems, establish material secretion systems, and increase the efficiency of production in animal cell systems.

(5) A variety of know-how has been accumulated during the 4-year period since starting full-scale biotechnological research. It is planned to place emphasis on:

Basic Gene Recombination Methods



1. Production of the useful proteins of human origin

2. Establishment of the technology for mass producing human monoclonal antibodies

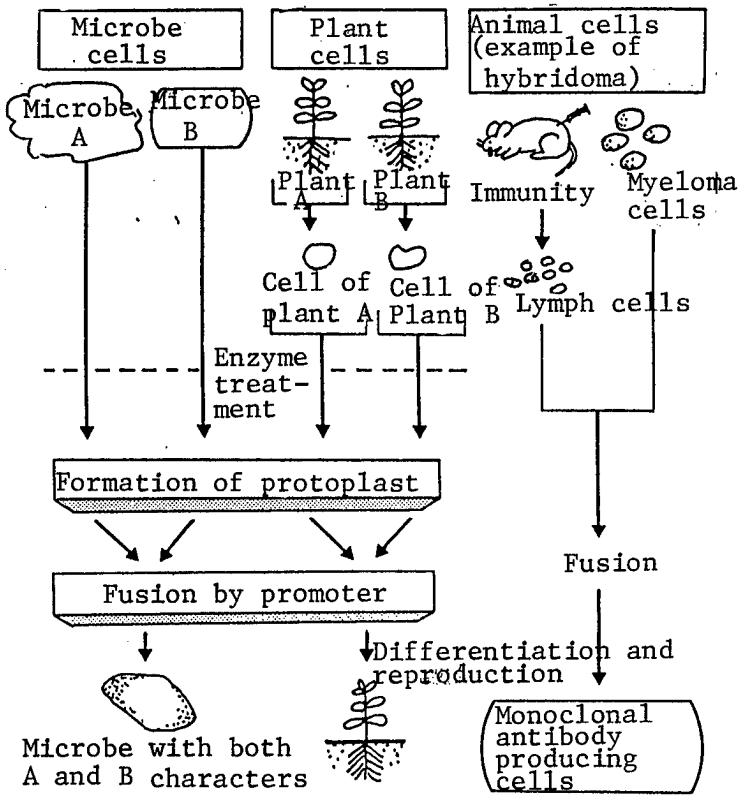
3. Development of new functional proteins

4. Production of antibiotic and other nonprotein materials

5. Cooperation for research in agricultural medicines, livestock raising, food, and fine-chemical sectors.

(Junshi Kakinuma, assistant manager)

Cell Fusion Processes



Dai-ichi Seed Company--Planning Office

(1) We are engaged in production, wholesale and retail, of the seeds and seedlings of flower petals and so forth.

We have therefore placed importance on the study and development of systems for no-disease mass-proliferation by culturing the tissue (growing point) of flower petals and of the media for this culture.

At present, the no-disease seedlings and bulbs of carnations, rhizocarpous babies' breath, (galiberra), gladioli, freesias, and so forth are being produced by tissue culture and sold.

(2) The research farm with an area of about 130,000 square meters (about 7,000 square meters for facilities) at Gotenba City, Shizuoka Prefecture, is carrying out the study and development of the above, part of an important process for producing no-disease seedlings, the new type of breeding mainly for flower petals, and study and development in a wide range of related sectors.

(3) We are carrying out development of no-disease proliferation systems and research on culture media, and adding methods for high-level breeding, for example, by embryo and anther culture, to the conventional ones for cross-fertilization breeding. In order to produce new plants at cellular and genetic levels, research and development is underway under a technical venture with Mitsui Petrochemical Industries for efficiently complementing both companies' agricultural and biological engineering functions.

(4) No-disease seedling and bulb mass proliferation systems have just started commercial production. It is an important task to reduce its cost by its improvement and increase the plants within the scope of their application.

We are planning also to efficiently increase and improve embryo and anther and other high-level breeding methods by use of the hitherto-improved technology of developing culture media and culturing tissues for mass proliferation.

(Kenichi Sakabe, manager)

Toray Industries--Research and Development Planning Department

(1) We started life science research about 10 years ago for the production of high-molecular materials adaptable to living bodies, for production of fine-chemicals by enzymatic and fermentation methods, the culture of cells and so forth. Therein we have successfully commercialized artificial kidneys, medical apparatuses, soft contact lenses, and amino acid L-lysin. Human-interferon-β will be put on the market in the near future.

(2) The Textile Research Institute, the Basic Research Institute, and the Development Research Institute are engaged in research on life science, the Development Division in its development, the Safety Laboratory in its safety, and the Engineering Research Institute in its engineering.

(3) Research subjects include pharmaceuticals, examination and diagnostic medicines, artificial kidneys, medical apparatuses and related units, and fine chemicals. Emphasis is placed on long-period basic search for useful materials.

(4) Many of the processes and produce developed therein require a long time for industrialization without infringing upon government regulation. Products are, on the other hand, compelled to a reduced life cycle because of severe competition in development and the rapid progress of science and technology. Research tasks are difficult to set up and are heavy risks. Interdisciplinary efforts are necessary and securing of staff is important.

(5) According to medium- and long-range technological prospects, we are planning to implement technology to develop the lines suitable for market needs. For the time being, this will put importance on acquisition of good results in biotechnology-oriented medical sectors as well as on their extension.

(Yasutaka Nishino, chief member)

Japan Roche Research Institute

(1) The pharmaceuticals, diagnostic medicines, vitamins, and agricultural medicines of our business lines are considered as included in life science subjects although it has not clearly been defined. They maintain close cooperation with overseas Roche groups in research.

(2) The Research Institute is engaged in search, research and development, the Development Technology Center in technological development, and the Development Center in clinical research and application to authorities. Less than 20 percent of total personnel is attached to them. This institute, established in 1972, consists of pharmacological, toxicity-pathology, biochemical, microbiological chemistry, applied microbiology, and molecular genetics divisions. The latter five are busily engaged in so-called new biotechnology.

(3) Among the various projects for the search, evaluation and development of unique, useful medicines, emphasis is placed on development of medicines for the aged, angiocardiopathy, pharmaceutics, and immunotherapy. The subjects of development now underway vary considerably, including hard-type medicines (anti-cancer medicines) and soft-type ones (BRM, etc., produced by biotechnology). Importance is attached to the search for fermentation processes and the genetic and cellular engineering approach to diagnostic medicines.

(4) Further progress is necessary for new biotechnology as well as its related and downstream technology. There are a number of problems to be solved in the evaluation and clinical development of the unique medicines not included among the conventional medicine categories. It is necessary in the near future to solve the problems of how to acquire, preserve, and maintain various kinds of microbes, bacillus stocks, and human tissues. Furthermore, medicines require the elongation of patent terms since a long period is necessary for their development.

(5) We are planning to put on the market the products of the categories mentioned in (3) in the near future. In particular as to new biotechnology, Japan Roche has already placed monoclonal-antibody diagnostic medicines on sale and made application for approval of industrialization of IFN-α, the first of its recombinant medicines. Furthermore, BRM, diagnostic medicines, microbe processes, and material production are expected to be successfully commercialized.

(Yasuo Yagi, manager)

Hayashibara Biochemical Laboratories--Publicity Planning Office

(1) Established in 1970 to further carry on Hayashibara's life science research and development in existence for many years. Succeeded in establishing unique "human-cell mass-proliferation method" by using hamsters, as well as developing and mass producing natural interferons in vivo not producible by existing gene recombination methods, and other antiviral agents as well as TNF, OH-1 and other antitumor ones.

(2) The Cellular Center was established this April (1985) to collect, preserve, and study various kinds of cells. It has already collected more than 400 kinds of cells. They are mass produced at Fujisaki Research Institute and different ones are fused to produce the hybridoma for discovering various physiology-activating materials.

(3) Our cell proliferation methods contribute to the mass production of antiviral and antitumor agents as well as hormones and other materials very useful for human bodies. Research is therefore underway to develop medicines in vivo. Also, we are planning the research for separating and purifying physiology-activating materials in NASA's space shuttle in the near future.

(4) We wish to offer its facilities for the communication and information exchange among researchers in life science as well as in other sectors, hoping they will contribute to the development of new combined technology.

We wish to establish cooperation with a wide range of research institutions in the world in carrying out technological development for contributing to mankind's welfare rather than monopolizing useful technology.

(5) Kibi Takahara Pharmaceutical Factory is now under construction with completion in the spring of 1986 in Kibi Highland Technopolis under Okayama Prefecture's project. We are planning the experimental production and mass production of activating and other medical materials at the factory.

(Yuji Yokoyama)

Fujitsu Research Institute, Atsugi Research Laboratory--Organic Material Research Department

(1) There is a possibility of establishing a new sector called "bioelectronics" when the superior functions of organisms are introduced into electronics. We are planning to acquire its basic technology in order to promptly cope with the trend of biotechnology. However, we do not intend its commercialization as yet.

(2) Fujitsu Institute is studying and developing new materials and devices. Fujitsu International Information Social Science Research Institute, on the other hand, is conducting information processing functions on both a system and material basis, grasping a living body as a system.

(3) Research is underway on biosensors that are said to be included among the most promising sectors of bioelectronics. Therein biomaterials and microbes are dealt with and the application of biotechnology is planned for developing their materials.

(4) The future development of bioelectronics is difficult to forecast. Most uses of "biochips" and "biocomputers" have not yet been clearly illustrated. Further progress of biotechnology and other technology is therefore necessary for their clear imagination.

(5) To grasp technological trends accurately, research will be continued in a wide range of sectors, including those now considered as not connected with electronics because the contrary may occur in the future.

(Toshiaki Kitakoji, assistant manager)

Meiji Seika Kaisha--No 1 Pharmaceutical Developmental Department

(1) We attach primary importance to life science in our food and pharmaceutical business for contributing to mankind's welfare and health. The accumulation of basic know-how is necessary for its progress. We are carrying out research on gene recombination, cell fusion, and bioreactors, setting up close cooperation with outside research institutions. We wish to play a significant role in the progress of biotechnology.

(2) The subjects and methods of biotechnology are diversified. The Central Research Institute, the Pharmaceutical Development Research Institute, the Biological Science Research Institute, and the Fermentation Technology Research Institute are making the best use of their specialty in their respective research, as well as cooperation including personnel exchange for increasing the efficiency of their joint basic research.

(3) 1. Gene recombination

Clinical testing is now underway on the interferon-gamma developed by using recombinant colon bacillus.

Study and development are underway regarding human oligopeptide that is mentioned in 2 and 3.

Development is being carried out as to the host-vector system of antinomyces. Research is underway for the mass production and conversion of antibiotics as well as for the recombination and manifestation of different kinds of DNA under MITI's Significant Technology Development Subsidy.

2. Hybridoma

A (senno) bacillus serum-type distinguishing agent has been put on sale and a pregnancy diagnosing medicine is being developed (monoclonal antibodies apply to both).

(4) Gene recombination still remains among the major sectors of biotechnology. Its object--human oligopeptide--generally has a C-end amide or a saccharic chain. To obtain it, it is indispensable to develop the host-vector system of human and other eukaryotes. We are therefore planning to use not only microbes but those also in research.

(5) 1. By 1990:

Start of the sale of interferon-gamma, defoliant (bialaphos) (gene recombination, microbe cell fusion) and various kinds of diagnostic medicines with monoclonal antibodies

2. By 1995:

Start of the sale of physiology-activating human oligopeptide with eukaryote host-vector system and the production and sale of gene recombination and bioreactor technology applied food material antibiotic conversions.

3. By 2000:

Start of the sale of medicines for the quick diagnosis of diseases (cancer and intractable heredopathias) by DNA probes.

(Shinji Nakadori, assistant department manager)

Snow Brand Milk Products Company--Pharmaceutical Planning Office

(1) We have accumulated the know-how related to life science in the course of the study and development of powder milks for puericulture, special ones for abnormal metabolism diseases, milk products, and fermented milks.

The Pharmaceutical Planning Office established in 1981 in our head office has carried on the commercializing of this know-how by applying biotechnology.

Also, the Biological Science Research Institute set up in 1983 as a research base in Ishibashi-cho, Tochigi Prefecture is carrying out the research on cell culture and gene handling.

(2) The office and institute are engaged in planning the development of pharmaceuticals and their research, respectively. They serve as the center of research and development in life science.

Three research institutes have been established to develop foods and the Zygote Transplantation Research Institute for research in freezing preservation and transplantation of zygotes.

(3) Research is underway to recombine genes and mass-culturing human cells for the mass production of physiology-activating glycoproteins. Its subjects include human erythropoietin, human lymphotoxin, and human tissue plasminogen activator (TPA).

(4) It is most important for mass producing physiology-activating glycoproteins to establish the technology of mass-culturing eukaryotes (particularly mammal cells) and stabilizing gene recombinant cells.

(5) Research is underway to develop human erythropoietin and TPA as pharmaceuticals. In particular, the latter is planned to start preclinical testing by 1987.

(Hirotaka Maruyama)

Wakunaga Pharmaceutical Company--Central Research Institute

(1) We started the application of genetic engineering in the production of pharmaceuticals. In 1981, Secretin, a medicine developed by our pioneer gene recombination technology, was praised by the Science and Technology Agency.

We have also developed EGF, put 2-5A on sale, developed a mouse monoclonal antibody, placed on the market an automatic DNA synthesizer jointly developed with Shimadzu Corporation, and carried out joint research on Rectin.

(2) A research and development system has been established for garlic as the main material of Kyoleopin and other medicinal plants. Furthermore, so-called plant biotechnology is being established for cullus culture, cell fusion, and plant culture. A research and development system has also been set up for developing useful materials by applying nucleic acid, peptide and other synthetic microbes, and dividing, purifying, and analyzing object materials.

(3) 1. Useful peptides

Selectin, EGF, IFN, etc.--mass production technology has already been established or industrialization is in progress. TNF is jointly being researched by three companies.

2. Reagents and diagnostic medicines

INF research reagents such as 2-5A as well as the automatic DNA synthesizer have already been put on the market.

3. Plant biotechnology

Becoming busy. The results of its research will be revealed in the near future.

(4) 1. Japan is far behind the United States with respect to the practical use of genetic engineering. The problem is how to get ahead of the latter.

2. A long period is necessary for the practical use of inventions. In this respect the problem is how to reduce research investment recovery cycles.

3. Selection of research subjects (materials) and search for new compounds.

4. Research on medicine transport systems.

5. Increase in development capacity.

(5) 1. Improvement in quality of existing technology

Application of DNA fixing technology and enrichment of the technology for mass producing and purifying useful peptide.

2. The Second International Symposium on Life Science will be held in the fall of 1986.

3. Prospects for industrialization

Medicines will be industrialized starting with research and diagnostic reagents. However, there still remains a number of problems to be solved until their full-scale sale can be started. We wish to apply our own technology to this if possible and make inroads into sectors other than pharmaceuticals.

(Tohru Fuwa, managing director and institute manager)

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CSO: 4106/5015

BIOTECHNOLOGY

MICROBIAL STRAINS FOR AMINO-ACID PRODUCTION USING GENETIC ENGINEERING

Tokyo BIO INDUSTRY in Japanese Feb 86 pp 13-23

[Article by Hitoshi Enei, chief researcher and assistant director, Basic Application Laboratory, Research Institute, Ajinomoto Co. Ltd.]

[Text] This paper describes the present status of the development of basic recombinant DNA technologies that are used in breeding microbial strains for amino-acid production; and, as examples of how these technologies are applied, it also discusses the present status of the development of breeding technologies of these various amino-acid producing strains, dividing our discussion in terms of three amino-acid production methods: the direct method, by which amino-acid is derived directly from sugar; the precursor method, by which amino-acid is produced from metabolic intermediary bodies, and the enzymic method, by which amino-acid is produced on the basis of enzymic reaction derived from synthetic substrates.

1. Introduction

Amino-acid is the basic building block of protein; it plays an important role, not to be replaced by other substances, in nutrition and in the area of physical properties. For this reason, the amino-acid industry has developed the application of amino-acid in various areas, including foods, medicine, feeds, and chemical synthetics. In so doing, the industry has grown to a point where it now occupies an important position within the chemical industry. It is said that the supply of amino-acid worldwide is about 450,000 tons annually, and that most of it comes from Japanese manufacturers or from technologies exported from Japan.

The manufacturing technology of amino-acid differs from one amino-acid to another, but can be divided roughly into three areas, depending on the method of production: (1) extraction, (2) synthetic, and (3) zymotechnic. The extraction method prevailed in the earlier years of amino-acid manufacturing, under which, amino acid was carefully isolated from protein hydrolyte. Later, the synthetic and the zymotechnic methods were introduced,

with the result that a specific amino-acid could be manufactured by a procedure most advantageous to its production.

One essential factor in the establishment of the zymotechnic method was the breeding and utilization of microbial strains that can produce and synthesize large volumes of amino acid. In the early years, the process of breeding microbial strains began with the collection of high-capacity strains found in nature, and with the establishment of proper conditions for their cultivation. Then, on the basis of the establishment of mutation technology, and of a better understanding of the regulatory mechanism of amino-acid production and synthesis, breeding methods that would rely on inducing nutrient-requiring and drug-resistant mutant stocks were carried out. Furthermore, as a technique that would genetically combine various characteristics obtained by means of mutation technology, the intracellular gene recombinant technology--including the character transformation, character induction, and cell fusion methods--was also established and applied to breeding procedures. The breeding technologies up to this point were all mutation reinforcing types at the level of chromosome DNA. Then, in the past few years, we began to use recombinant DNA technology as a means of amplifying superior characters, using plasmid; this had led to a new development in breeding procedures. When we look at examples of how we apply recombinant DNA technology, we see that there are two aspects to it. In one, where the principle behind the procedure is one of assigning new functions to microorganisms and producing substances that these organisms cannot produce themselves, the method involved is one of producing proteins and peptides, which are the direct products of genes that were introduced. In the other, the method involved is one of amplifying the capabilities innate to the microorganisms. The concept involved in this second method is one that applies when amino-acid producing microbial strains are being bred. In other words, in the method that is based on this concept, genes that participate in the enzymes that produce and synthesize amino-acid in microorganism are first linked to plasmids. Then the genes which character-convert these links to amino-acid producing microbial strains and which hold them as targets are amplified. In this way, the method based on the second concept raises the volume of enzymes formed and makes amino-acid production more efficient. The recombinant DNA technology is used for more than just breeding microbial strains and applying directly to zymosis. Today, in combination with immobilized enzymes and technologies that utilize microbial strains, capable cultured strains, bred by recombinant DNA technology, and enzymes are being used as bioreactors. The range of its application is expanding.

In this article, I shall discuss the status of the development of basic recombinant DNA technologies for breeding amino-acid producing microbial strains; and, with regard to examples of how these technologies are being applied, I shall discuss them according to methods of amino-acid production as follows: the direct zymotechnic method (by which target amino-acid is obtained directly from sugar through fermentation), the precursor method (by which target amino-acid is produced/fermented from metabolic intermediary bodies), and the enzymic method (by which target amino-acid is produced in response to enzymic reaction of synthetic substrate).

2. The Status of the Development of Basic Technologies

In recombinant DNA technology, we extract DNA from gene-supplied microbial strains, cut it off with restriction enzyme, and link it to an appropriate vector to form a plasmid. The plasmid is then character-transformed onto a host strain to reveal and amplify the genes. These operations must be carried out smoothly, and, moreover, the genetic characteristics of the character-transforming strain must remain stable. It is for this reason that various improvements are being made in this area.

2.1 Genetic Materials

In recombinant DNA technology, the important genetic materials are the genes that participate in the enzymes that produce and synthesize amino-acids and the genetic marker strains. How these materials can be formed or obtained will determine the outcome of R&D. In particular, decontrolled genes and inhibition-removed genes are preferable in the technologies we are concerned with here. The reason for this is that in many cases, because structure-genes are linked to revealed-vectors, repression is reduced by gene-amplification.

As for the breeding of amino-acid producing microbial strains, various strains have been thus far examined on the basis of mutation technology, and highly productive strains are being induced. The strains that have been studied include Brevibacterium, Corynebacterium, Bacillus, Escherichia, and Sarratia. Furthermore, we now know a great deal about the metabolic control system of these strains, and are beginning to get a clearer view of the characteristics of their genes as well as their decontrol conditions. I believe that the utilization of information of this sort and genetic materials will be extremely helpful. In addition, there is an extensive accumulation of microorganismic genetics data and materials, for example, on Escherichia coli K-12 strain and Bacillus subtilis M strain. I believe that these data and materials will also be helpful, and, are, in fact, beginning to be utilized.

2.2 Host Strains

At present, representative strains used in breeding amino-acid producing microbial strains by recombinant DNA technology include Escherichia coli K-12, Bacillus subtilis M, Bacillus subtilis K, Brevibacterium lactofermentum, Corynebacterium glutamicum, and Serratia marcescens. A host strain weakens the activity of a microbial strain's external nucleic acid analysis enzyme in order to raise the frequency of plasmid's character conversion, and the activity of restriction enzyme which it possesses. It is, furthermore, necessary to breed the host strains in a manner that will not cause the plasmids incorporated into the cells to recombine and will not subject plasmid DNA's to change or be modified within the cells. Furthermore, when the protoplast method is used for character conversion, as in some microbial strains, it is necessary to increase the frequency of reproduction from protoplast to normal strain; progress is being made in this area.

2.3 Vector

We are developing vectors that are unique to specific host microbial strains. It is important that vectors can transport genes to host strains in a stable manner, and necessary for us to develop vectors with high character conversion frequency. In order to reveal genes effectively, we need to develop high revelation vectors with improvements in such areas as the promoter; and to develop vectors which can use both high and low copy counts in accordance with host strains. Also, as the number of genes increases, the size of a vector becomes problematic, so that we need to miniaturize the vector, and develop a harmonious vector that can distribute genes among several vectors. Recently, various vectors which meet these needs have been developed. (Table 1)

Table 1. Host/Vector Series and Examples of Their Application

Host	Vector	Amino-acid/enzyme production
E. coli K-12	pBR 322 pML 31 pSC 101	Thr, Phe, Pro, Trp, Lys, Tryptophan synthetase, Aspartase, ACLracemase
B. subtilis K	pUT 32	His
Brev. lactofermentum	pAM 330 pAJ 224	Thr, Pro PEP·carboxylase
C. glutamicum	pCG 11	Thr, His, Phe, Ile
S. marcescens	pKP 1155	Thr, His, Pro Aspartase

2.3.1 E. coli K-12 Strain

Various sectors are being utilized for the E. coli K-12 strain, of which pBR 322 and pBR 328 are representative; low copy plasmids such as pSC 101 and pML 30, derived from mini F, are also being used. Various high revelation vectors are also being developed, including such promoters as lac-UVS, trp, λPL, Lpp, tuf B, tac, Omp F, γγB, bla, as well as combinations of these. In an effort to stabilize plasmids, there are a number of cases[1] in which various plasmids are combined or DNA derived from mini F is being incorporated. As an outstanding example, Miwa, et al.,[2,3] using an antibiotic dependent strain (Sm^d) as a host, have developed a method of covering this dependability onto a vector and placing a gene that converts the host strain into one of antibiotic independency (Sm^{id}). Under this system, plasmid-less strains grow only when antibiotic (Sm) is added and, under antibiotic independency, the plasmid-less strains do not grow, but those with plasmid do (Figure 1).

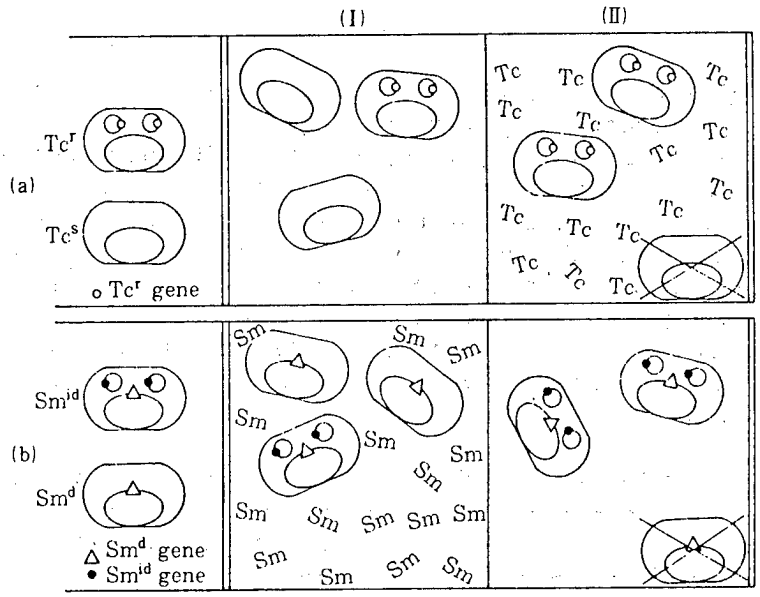

Figure 1. Stabilization of Plasmid Holding Strains by Antibiotic Dependency Variation Application

Tc: Tetracycline r: resistance s: sensitivity
Sm: Streptomycin d: dependency id: independency

(a) Antibiotic annexing method (b) Method applying variation in antibiotic dependency (I) Selection pressure independent conditions (II) Selection pressure dependent conditions

At (I), breeding of plasmid-less strains is possible, but (II) shows selection and discarding of plasmid-less strains. For explanation, refer to the text.

2.3.2 B. subtilis M Strain, B. subtilis K Strain

For these strains, many plasmids such as pUB 110, pTP4, etc., have been developed and used. In the case of B subtilis K strain, since neither pUB 110 nor pTP4 can be used, Kawashima, et al.,[4] created a compound plasmid pUT 32 by extracting the copy starting territory and the chloramphenicol resistance (CM^r) territory with restriction enzyme XbaI, and by incorporating these into kanamycin resistance (Km^r) plasmid pUB 100. The pUT 32 has a molecular weight of 4.5 Md., possesses Cm^r and Km^r, has good character conversion efficiency, is held stable within the K strain, and is used to breed amino-acid producing microbial strains.

2.3.3 Brev. lactofermentum Strain

Sano, et al.,[5] discovered plasmid pAM 330, with an unknown selection marker, from Brev. lactofermentum ATCC 13869. The molecular weight of this plasmid was 30 Md, its estimated number of copy about 10, and one location was cut

off by Bgl I and others. Furthermore, Yamaguchi, et al,[6] have already determined the entire base configuration of pAM 330, and Sano, et al.,[5] have linked pAM 330 with E. coli derived pBR 325 to create pAJ 655, which they miniaturized to form pAJ 43 (Cm^r). Takagi, et al.,[7] have extracted a Tp^r region from the chromosome DNA of trimetoprium resistant (Tp^r) mutant strain AJ 12146 of Brev. lactofermentum and induced it into pAM 330 to create pAJ 228. And from pAJ 228, the same team has also created pAJ 224, possessing Pst I, Sal I, and Bam HI, as a cloning region with one section cut off. This pAJ 224 is Tp^r, 3.6 kb large, and about 60 copies per cell exist; its stable maintainability has been acknowledged, and it is being used in breeding amino-acid producing microbial strains.

2.3.4 C. glutamicum Strain

Katsumata,[8] Ozaki,[9] et al., have sought plasmid in C. glutamicum strains found in nature, and have obtained from them pCG 4 (29 kb) with a low copy number and pCG1 (3.05 kb) and pCG 2 (6.6 kb) with high copy numbers, all possessing streptomycin (Sm), spectinomycin (Sp) resistant genes. Furthermore, by linking plasmid derived from pCG 4 with pGA-22 derived from E. coli, they were able to create a shuttle vector. This shuttle vector has a restriction enzyme with one cutoff region, and is recognized as being able, by means of C. glutamicum, to character-reveal genes and drug resistant markers derived from E. coli. It is also used in breeding amino-acid producing microbial strains.

2.3.5 S. marcescens Strain

Initially, Sugiura, et al.,[10] were using and studying pACYC-177 and pBR 322, but later switched to pLG 339 (Km^r, tetracycline resistant (Tc^r)) derived from low copy pSC 101 and pKP 1155 (ampisirin resistant (Ap^r)) derived from mini F of E. coli. However, since pKP 1155 is not always stable, they created pKP 1124 by linking miniaturized plasmids of pKP 1155 with Km^r genes of pKT 240, and are uisng it for breeding amino-acid producing microbial strains.

3. Application to Breeding of Amino-acid Producing Microbial Strain

There are, roughly speaking, three zymotic methods: 1) the direct method using sugar, 2) the precursor method using metabolic intermediary bodies, and 3) the zymotic method using enzymic reaction of synthetic substrates. The application of recombinant DNA technology differs, however slightly, depending on which one of these three methods is used.

3.1 Direct Zymotechnic

In the direct zymotechnic method, in which amino-acid is produced directly from sugar, it is necessary to amplify and reinforce not only the enzymic genes of the solid amino-acid series, but also those of its co-series, the sugar metabolic series.

3.1.1 Threonine Producing Microbial Strain

Miwa, et al.,[11,12] prepared a compound plasmid from pBR 3222 and chromosome DNA of Thr producing β-IM 4 (α-amino-β-hydroxyvalerian) acid resistant (AHV^r), Ile demand, Met demand, Pro demand (thymine demand) derived from E. coli K-12 strain. The plasmid was then character-converted to Thr demand strain derived from β-IM 4, and character-converting strain, which has recovered its demand function, was selected. The character-converting strains obtained in this manner not only indicated AHV^r, but simultaneously, showed higher Thr accumulation than in their parent strains. No 294 was obtained by modifying the 7.8 Md plasmid and introducing it, along with Thr genes obtained in the manner described above, into β-IM 4 strains of the Thr nondemanding type. This No 294 strain could produce and store 13.4g/ℓ (about 40 percent anti-sugar absorption rate) of Thr. This plasmid pAJ 294 has the entire operon (thr A, B, C) of Thr producing gene incorporated into it, has an intracellular copy count of 12, and the activity of its Homoserine denydrogenase that is coded into thr A has been raised to about five times that of parent strain (Figure 2).

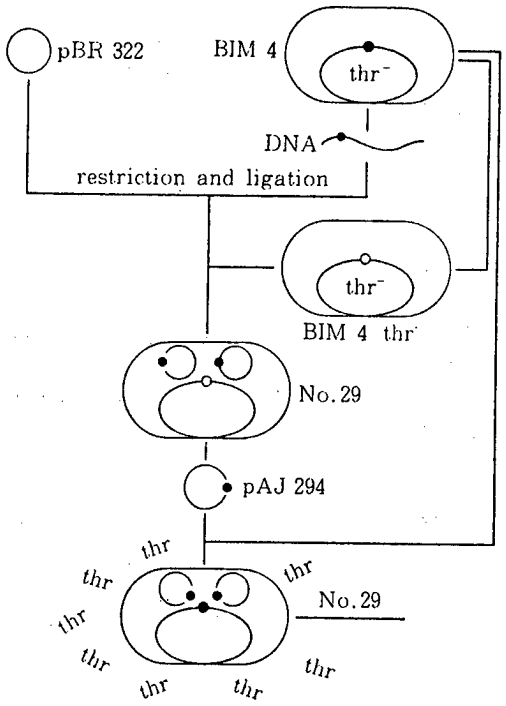

Figure 2. Breeding of Threonine Producing Microbial Using Recombinant DNA Method

Shimizu, et al.,[13] furthermore, have examined the cultural conditions of No 294 strain in a small jar. They found that by maintaining a comparatively high oxygen density of the culture solution, they could control the microbial growth, increase the enzymic activity, and succeed in obtaining a high accumulation--65 g/ℓ--of Thr.

Morinaga, et al.,[14] cloned HD genes and Homoserine Kinase (HK) genes with Thr producing M-15 strains, which, as DNA providing microbial strains, were derived from Brev. lactofermentum. These HD and HK genes were linked respectively with plasmids pAJ 1844 (CM^r) and pAJ 224 (Tpr), and pAJ 210 and pAJ 212 were induced. These two plasmids were made to coexist in Thr producing microbial strains and made to reveal. It was then discovered that HD activity of character-conversion strain increased by 4 to 14-fold, HK activity by 22 to 29-fold, Thr productivity from 25 g/ℓ to 33 g/ℓ, and that volumes of accessory Lys and Hse decreased.

Ito, et al.,[15] cloned Phosphoenol Pyruvate Carboxylase (PEPC), a sugar metabolic enzyme, by using Brev. lactofermentum. When pAJ 201, with PEPC genes, was introduced into Thr producing M-15 strain, the PEPC activity increased by 1.5-fold, the Thr productivity by 12 percent. Again, when this pAJ 201 was introduced into Pro producing strain AJ 11225, the Pro productivity improved by about 71 percent. Accordingly, the reinforcement of PEPC is an example of how productivity was improved by reinforcing common amino-acid producing series.

Kusamata, et al.,[16] have created the shuttle vector pE thr 1, which combines Thr operon that codes 4 genes derived from E.coli K-12 strain--Asparto Kinase (AK), HD, HK, Threonine Synthetase (TS)--into C. glutamicum vector pCG 11 (Sp^r). Furthermore, they applied mutation procedures that give AHV^r to this pE thr 1 to induce pE thr 115, and introduced it to Thr producing microbial strain, C. glutamicum Ky 10440. The Thr productivity increased from 5.6 g/ℓ to 21 g/ℓ.

Komatsubara, et al.,[17] linked chromosome DNA fragments, obtained from S. marcescens Sr 41-TLr 156 strain that is free of AK and HD interferences, with pLG 339, and cloned them with E. coli derived C-600 strain (thr B^-) as a host. The pSK 301 obtained in this manner included the entire thr operon territory. Next, when they introduced this pSK 301 into S. marcescens Sr-41 strain found in nature, the HD activity increased 4 to 5-fold. Again, when this pSK 301 was introduced into Thr producing T-1165 strain, about 60 g/ℓ of Thr was produced in a cultural mix which was comprised mainly of sucrose and urea.

3.1.2 Histidine Producing Microbial Strain

Kawashima, et al.,[18] cloned His producing microbial strain B. subtilis KAJ 12111 (triazole alanine resistant (TA^r)), 5-fluoro-tryptophan resistant (5-FT^r) as a DNA donor strain, and obtained pAH 3, which complemented His demand of his J lacking strains of B. subtilis M strain. When, from this pAH 3, fragments, including his J, were combined into vector pUT 32 (Cm^r, Km^r) that is used for B. subtilis K strain and introduced into His producing AJ 12111 strain of K, the His productivity increased from 6.3 g/ℓ to 8.8 g/ℓ. The AJ 12111 is a strain which is freed of His control vis-a-vis Phosphoribosyl-ATP-Pyrophosphorylase; it is believed that the productivity rose because his J was reinforced by the introduction of plasmid and because Histidinol dehydrogenase was also reinforced.

Minakami, et al.,[19] created a plasmid that includes E. coli derived genes his G, D, C, and B by using E. coli K-12 and C. glutamicum shuttle vector. Using this plasmid, and by means of complementarity study, they were able to obtain his G^- strain from C. glutamicum His demand strain. Again, using this his G^- strain as a host, they cloned his G from C. glutamicum DNA found in nature, and created pChis G. In order to remove interferences due to His of ATP-Phosphoribosyl transferase, they separated pChis G^{tra}, which is 1, 2, 4-triazole-3-alanine resistant (TRA^r), from pChis G. When this pChis G^{tra} was introduced into His producing strain, the His productivity increased from 7.6 g/ℓ to 15.3 g/ℓ.

Sugiura, et al.,[10] linked chromosome DNA of His producing MPr 90 strain of S. marcescens with pLG 339 (Km^r), and obtained pSS 101(5.1 kb) which complements his G^-. From pSS 101, they extracted Eco RI fragment 4.7 kb and subcloned it to pKT 1124 (derived from mini F, Km^r, Ap^r) to obtain pSS 503. When pSS 503 was introduced into His producing MPr 90 strain, the His productivity increased from 23 g/ℓ to 36 g/ℓ. From the fact that enzymic activities of G, D, C, and B of this strain increased by about two-fold, it was understood that his G, D, C, and B were included in pSS 503. Furthermore, when this pSS 503 was introduced into His producing L 120 strain, the His productivity increased from 28 g/ℓ to 41 g/ℓ.

3.1.3 Phenyl Alanine Producing Microbial Strain

Yabuta, et al.,[20] extracted phe A, that codes chorismate mutase and prephenate dehydratase genes, which, in turn, are the key enzymes of the Phe producing and synthesis series, from pKB 45 that Zurawsky and others had created.[21] After the extracted phe A was inserted to pSC 101 and introduced into E. coli K-12 strain, it was subject to mutation treatment to obtain interference-free phe A gene. Taking advantage of the fact that λ phage P_RP_L promoter at revelation receives temperature adjustments due to the existence of a heat sensitive repressor derived from CI_{857}, Yabuta and others inserted phe A in the dowstream of P_RP_L, created pSY 110-5, and obtained a character-converted strain. As a result, the Phe productivity increased along with the rise in the temperature of the culture, so that at 38°C, they were able to accumulate 0.15 g/ℓ of phe. At temperatures above 40°C, the productivity declined due to host cells hindering the multiplication process. Furthermore, Sugimoto, et al.,[22] were able to extract aroF genes, that codes 3-deoxy-^{D}-arabinoheptulosonate-7-phosphate synthetase (DAHP synthetase), from Zurawsky's pKB 45, insert them into pSC 101, and created pSY 60-5. By inserting this into E. coli AB 3257 and subjecting it to mutant treatment, they were able to obtain interference-free aroF gene, and ultimately the pSY-60-14. They, then, created various plasmids in which were distributed the previously extracted phe A and the aroF. The plasmids were introduced into E. coli CGSC 4510 (thi^-, tyr A) strain, and after obtaining character-converted strains, the Phe productivity was examined. As a result, the phe accumulation increased from 0.5 g/ℓ to 0.96 g/ℓ when plasmids with aroF were introduced; and, by using a small fermentation bath and slowly adding glucose, the source of carbon, a phe accumulation of 14.5 g/ℓ was obtained.

Ozaki, et al.,[23] linked chromosome DNA fragments of C. glutamicum K-38 with pCG II (Sp^r), and conducted cloning of phe productivity related genes. As a result, they were able to obtain character-converting strains possessing Sp^r and PFP^r. Because the plasmids obtained here complemented the dual demands of Phe and Tyr, both of C. glutamicum KY 9456 strain, and, at the same time, offered PFP^r to KY_{9456}, it was confirmed that these plasmids contained Chorismate mutase genes. When this plasmid was introduced into phe producing strain, the phe productivity rose by about 60 percent, and a maximum accumulation of 19 g/ℓ was obtained.

Ikeda, et al.,[24] noting that the phe A gene of E. coli could code Chorismutase mutase (CM) and Prephanate dehydratase (PD) of the phe production and synthesis series, experimented with the breeding of E. coli phe A gene by introducing it into C. glutamicum. In other words, they subcloned the E. coli phe A onto the shuttle vector pCE-51 of E. coli-C. glutamicum, created a pE phe A-1, and introduced it into C. glutamicum. As a result, the activities of CM and PD increased by 5 to 9-fold, and the fact that E. coli could be revealed in C. glutamicum was confirmed. Since the CM and PD activities of this E. coli phe A are subject to interference by phe, the researchers collected PFP^r to obtain pE phe A-22. When this pE phe A-22 was introduced into the producing strain, the phe productivity increased from 10 g/ℓ to 13.7 g/ℓ. In addition, while CM-PD activities of pE phe A-22 were completely free from phe interferences, the CM/PD enzyme production of pE phe A-22 was controlled under the presence of phe, so that the effect of attenuation is being hinted at.

3.1.4 Proline Producing Microbial Strain

Siewert, et al.,[25] obtained dehydroproline resistant (DP^Y) strain from E. coli, and, after having desensitized γ-Glutamyl-Kinase, succeeded in simultaneously cloning the pro A, B, and C of this strain. By introducing this compound plasmid into DP^r strains, they were able to obtain highly productive Pro strains. While the parent strain could only accumulate 3.1 g/ℓ of Pro, the introduced strain accumulated 13.8 g/ℓ.

Imai, et al.,[26] linked chromosome DNA fragments of Pro producing DTAr-80 strain with pKP 1155 (Ap^Y) derived from mini F, and obtained pYJI 333, which complements Pro demand strain HB 101 derived from E. coli ($pro\ A^-$). They induced pYI 350, which is more stable than pYI 333. By introducing this pYI 350 into Pro producing DTAr-8 microbial strain, they obtained character-converted DTA-8 (PYI 350) strain. When they examined the productivity of Pro, they noticed that it rose from 50 g/ℓ to 75 g/ℓ.

3.1.5 Isoleucine Producing Microbial Strain

Katsumata, et al.,[27] using a shuttle vector between E. coli-C glutamicum, were able to obtain, from chromosome DNA of C. glutamicum T 106 strain found in nature, pC hom 9, by cloning Sal I DNA fragments which complement Hse demand (HD deficient) of T 106 substrain RRL 5011. From the fact that pC hom 9 can restore the HD deficiency of E. coli Gif 102, it was confirmed that it does in fact include HD genes. The pC hom 9 introduced strains of

C. glutamicum showed, by the action of Hd amplification, a high level of AHV^r. By mutation treatment of KLS 4 (pC hom 9), which has a relatively low degree of AHV^r resistance, the researchers were able to obtain pC hom 17 given by AHV^r. When this pC hom 17 was introduced into Ile producing C. glutamicum TDA-25 strain, the Ile accumulation at TDA-25 was 4.6 g/ℓ, while at TDA-25 (pC hom 17) it was 8.4 g/ℓ. By reinforcing the amplification of HD, they were able to increase the Ile accumulation.

3.1.6 Lysine Producing Microbial Strain

Leverend, et al.,[28] using the E. coli mutation strain TOR-21, whose AK III is structural and desensitive, extracted genes asd, dapA, dapB, and lysA--corresponding respectively to Aspartate semialdehyde-dehydrogenase, Dihydrodipicolinate synthase, Dihydrodipicolinate reductase, and Diaminopimelate decarboxylase--and linked them to pBR 322. Having, then, created such compound plasmids as pADI, pDAI, pDB2, and pLA 17, they character-converted to their parent strain, TOCR-21. As a result, the enzymic activity of various character-converted strains rose by about 10 to 20 percent. When pDAI was character-converted, however, the Lys growth increased about 1.5 percent, and only 6.5 g/ℓ of Lsy was accmulated.

3.2 Application to Precursor Method

Because, unlike the direct enzymic method that uses sugar, the precursor method depends on zymotechnic to produce amino-acid from intermediary bodies precursors of the production-synthesis series, less genes are involved than in the direct method. This makes it easier to apply recombinant DNA technologies to improve breeding procedures.

3.2.1 Production of Tryptophan From Anthranyl-Acid

Aiba, et al.,[29] using a Trp repressor (trp R) and Tryptophanase deficient E. coli as a host, obtained Trp producing microbial Tna/pSC 101-trip, by character-converting a compound plasmid that has trp operon linked with pSC 101. Then, by offering 5-methyltryptophan resistant ($5\text{-}MT^r$) to this Tna/pSC 101-trp strain, they obtained a trip I mutant plasmid, whose desensitivity differs vis-a-vis interferences caused by Anthranyl synthase-Phosphoribosyl-anthranyl transferase enzymic compound (trp E,D), and succeeded in breeding Trp producing tna/pSC 101-trp 115 microbial. As for this microbial strain's Trp productivity, 6.2 g/ℓ of it was accumulated during 72 hours of culture. This was done by initially adding 0.5 g/ℓ of anthranyl-acid, then, when the acid was consumed down to 0.3 g/ℓ, by resupplying the acid continuously at about 5 mg/ℓ/hr.

3.3 Application to Enzymic Method

This is a method by which amino-acid is produced from synthetic substrate by enzymic reaction. Since all that is involved is the mass production of single enzymes by using recombinant DNA technology, this technology can be most easily applied here. Recently, furthermore, there have been developments in bioreactor technology, so that we can expect big improvements in this production method.

3.3.1 Production of Asparaginic Acid From Fumaric Acid

Aspartase is an enzyme which acts as a catalyst in the formation of Asp from fumaric acid and ammonia, and is available commercially.

Taniguchi, et al.,[30] took advantage of the fact that, in E. coli, Aspartase deficient strains could be obtained by examining mutant strains which cannot grow on Glu as the sole source of carbon; and, using Glu demand strain as a host, performed cloning by the "shotgun method" from DNA of E. coli K-12 MM 294 strain. At that time, when pBR 322 and pBR 325 were used as vectors, no cloning was obtained. But when low-copy pSC 101 was used as a vector, clones of Glu^+ were obtained, some of which were Aspartase active. One of these strains was about four times as active as the control strain TK-6.

In addition, Takagi, et al.,[31] were able to collect Ap^S strains, that are deficient in extra-cellular nuclease and restriction enzyme, from S. marcescens strains found in nature. This mutant strain had a high character-conversion frequency, and recombinant DNA work could be easily performed on it. Using Aspartase deficient strain of E. coli K-12, they searched for pACYC 177-aspA and obtained pVT 104 (approximately 16 kb). Subcloning asp A, they also obtained pVT 150 (pBR 322-asp A, approximately 6.6 kb). When pVT 150 was introduced into S. marcescens 8,000 strain found in nature, the Aspartase activity increased by about 20-fold.

3.3.2 Production of Lysine From α-Amino-ε-Caprolactam

We are already aware of the reaction which produces Lys from α-amino-ε-caprolactam (ACL). In this reaction, ACL-Racemase is an extremely important enzyme in utilizing the DL-ACL substrate.

Yanai, et al.,[32] linked 3-10 kb of DNA fragments, obtained by sectionally decomposing and dividing chromosome DNA of Ach. obae with restriction enzyme, with pBR 322, and introduced them into E. coli MM 294 Lys. They looked for clones that could grow in a culture that does not include Lys, but does include L-ACL hydrolysis enzyme and D-ACL. They, then, shortened the DNA fragments of 9.3 kb Ach. obae cloned in the manner just described using restriction enzyme; linked the fragments to various vectors derived from E. coli; obtained character-converted strains, and measured their Racemase activity. While the activity of E. coli Racemase, containing pNN 3 in which 9.3 kb NDA has been incorporated, was less than 10 percent of that of DNA providing strain, it rose by 3-fold when 4.2 kb DNA fragments obtained by cutting off Eco RI from pNN 3 were linked with pACYC 184. What is more, structural production became possible.

3.3.3 Production of Phenylalanine From Cinnamic Acid

Phenylalanine ammonialyase (PAL) breaks down Phe into cinnamic acid and ammonia, but it is known that by reverse reaction Phe can be reconstituted, and this fact is being applied as one means of producing Phe.

Gilbert, et al.,[33] are experimenting with the cloning of Rhodosporidirem toruloides genes with E. coli K-12. They have created an R. toruloides gene library using λ1059 bacteriophagy, and are identifying PAL genes using ^{32}P-cDNA. As a result, they discovered that PAL genes, as PAL-mRNA, are 2.5kb long; they are continuing with the isolation of these genes, and the breeding of character-converting strains.

Hamilton, et al.,[34] bred microbial strains, in which PAL genes from Rhodotorula rubra had been linked to plasmid and which have been amplified; and, using the strains' whole cell and by means of an inclusion method, fixed these strains and created a bioreactor. As substrates, they used ammonia 7.85 M and cinnamic acid 0.37 M, and made them react to produce Phe 0.35 M (59 g/ℓ).

3.3.4 Production of Serine From Glycine

Kotani, et al.,[35] noting that Serine hydroxymethyl transferase (SHTase) acts as a catalyst in the Gly + HCHO → Ser reaction, studied the amplification and reinforcing of Ser producing enzyme from Gly by using recombinant DNA technology. In other words, they created a pKS-6, which complements gly A, by linking chromosome DNA fragments of E. coli with pSC 101 and by introducing the link into E. coli G-17 (gly A$^-$). They also created pBR 322-gly A by transferring Eco RI DNA fragments from this pKS-6. The G-17 strain possessing this pBR 322-gly A increased its SHTase activity by about 60-fold. When, using this microbial strain and under cell free condition, Ser production from reaction was checked, about 1.3 g/ℓ of Ser was produced.

Hamilton, et al.,[34] have also obtained gly A containing pGX 139, by linking E. Coli DNA fragments with pBR 322, then by obtaining DNA fragments that complement gly A, and finally by subcloning the latter and linking them with pGX 145. They have also character-converted pGX 139 onto K. aerogenes. They, furthermore, report that gly A promoter is stronger than λ_{PL} or trp/lac hybrid promoter, and that it produced enzyme protein up to 10 percent of microbial protein. Still further, they are studying the possibility of a bioreactor for Ser production. Since the substrate formaldehyde deactivates SHTase, it is necessary to perform "feeds" during reaction periods and at a low level. And, since supplementary enzyme THF is extremely susceptible to oxidization, reactions should preferably take place under conditions of reduction. When formaldehyde is automatically fed at low levels and THF is given in sufficient doses under reduction conditions, the Ser production speed was 10 g/ℓ/hr, and more than 400 g/ℓ of Ser was accumulated (Figure 3).

3.3.5 Production of Tryptophan From Indol

It is already known that both Tryptophan synthetase and Tryptophanase produce Trp from either Indol and Ser or from Indol, pyrubic acid, and ammonia. Attempts are being made to strengthen these enzymes using recombinant DNA technology.

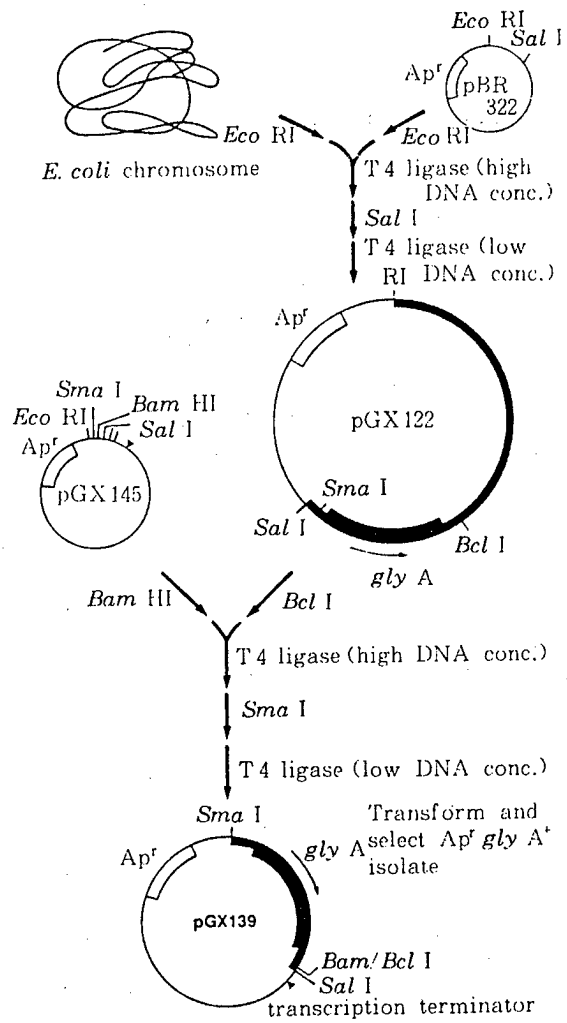

Figure 3. Cloning of E. coli gly A Genes

Yukawa, et al.,[1] are trying to strengthen Tryptophan synthetase. They are introducing trp operon and mini F into pBR 322, and character-converting it onto E. coli. They have cultured character-converting strains under Indol ascetic acid conditions and collected microbials as enzymic source. By reacting 11 g of Indol (initially 5 g, later fed at appropriate intervals), 15 g of L-Ser, and 5 g of intact cells of character-converting strains to 16 hours, they were able to accumulate 180 g/ℓ of Trp.

Anderson, et al.,[36] knowing that β_2-subunit of Tryptophan synthetase can produce Trp from Indol and Ser, extracted trp A and B genes, linked them with plasmid in the form of trp/lac hybrid promoter, and introduced them into E. coli. The enzymic activity of character-converted strain increased by about 230-fold, and about 20 percent enzyme per microbial protein was produced. Using this microbe as enzymic source, they produced and accumulated about 78 g/ℓ of Trp from Indol and Ser.

Hamilton, et al.,[34] created pGX 2236, which combines trp operon and gly A, from plasmid pGX 110, which contains trp operon, and from pGX 139, which contains gly A gene that plays a role in serine production. Having created this, they introduced it into E. coli. Using this character-converted strain, they created a bioreactor and are studying the growth of Trp. Ser grows from Gly and formaldehyde at the collection rate of 84 percent against Ser; Trp grows at the collection rate of 95 percent against Indol, 93 percent against Ser, and can be produced continuously. They have reported that using the batch reaction they produced and accumulated 200 g/ℓ of Trp.

4. Conclusion

I have thus far discussed the present status of the development of basic recombinant DNA technologies as they apply to the breeding of amino-acid producing microbial strains and of the application of these technologies in the breeding of these strains. As can be gleaned from the examples given above, I will not be overstating if I were to say that we are still at an experimental stage. Moreover, as these examples again indicate, it is not the case that superior amino-acid producing microbial strains can be obtained by recombinant DNA technology alone. In other words, we need to have more genetic analysis of the induction of control removal strains as done through mutation technology, which is our basic technology; of the regulatory mechanism of amino-acid production and synthesis series; and, of the construction of gene maps that indicate the existence of genes. We also need more involved technological developments in recombinant DNA technology, including the technology to extract genes and link them to multiple genes, the method to reveal linked genes efficiently, the technologies in the handling of promoters, terminators, and attenuators, and the technology to stabilize plasmids. Further still, we need more studies in the cultural engineering of microbial strains that have been bred through recombinant DNA technology. Accordingly, there are numerous aspects of this recombinant DNA technology as it applies to amino-acid breeding which still must be developed. Each of these must be resolved before any success can be achieved. Consequently, in order to advance these technologies greatly and make their impact felt more powerfully, we still need to accumulate our stock of basic knowledge, and continue with our research.

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9711/9365
CSO: 4306/1163

TELECOMMUNICATIONS

INFORMATION-RELATED POLICIES FOR FY 1986 REPORTED

Tokyo DENSHI KOGYO GEPPO in Japanese Vol 27 No 10, 1985 pp 10-17

[Article by Norimiki Ito of the Electronics Policy Division, Machinery and Information Industries Bureau, Ministry of International Trade and Industry: "Important Points of Information-Related Policies for the Fiscal Year 1986--Springboard to High-Information Society."]

[Text] Prologue

Implementation of information society in our country is favorably advancing as shown in the rapid spread of electronic computers (the number of operating electronic computers at the end of December 1984 was 172,533 sets). In order for our national economy to continue the stable growth for the medium- and long-term future, realization of a sound high-information society based on the extensive advance of information implementation not only in the industrial field but also in national life is necessary. For this purpose, the solution of the problem of more basic information-utilization infrastructure is requested based on the diversified requirements in various fields of society. In other words, countermeasures for the problems, which support the information society such as training of personnel, implementation of software supplying infrastructures and establishment of data bases, have become important.

The deployment of the projects, in which the establishment of the information-related infrastructure is emphasized, will realize the high-information society, which will bring about the enhancement and vitalization of an industrial structure and pleasant and enriched national life, and will also secure stable investment in equipment, which is at present the most important problem in our national economy and will enhance the expansion of domestic demands.

MITI will continuously promote the integrated information-related projects in fiscal 1986 based on the viewpoints described above.

1. PROMOTION OF INTEGRATED PROJECT THAT FACILITATES SOFTWARE SUPPLY

Countermeasures for Education and Personnel Training in Information Utilization

In order to realize the high-information society corresponding to the diversified needs in industrial and social fields, it is urgent to train personnel which support information-related activities in the various fields of industries and society. For this purpose, integrated countermeasures for personnel training and education of information utilization will be implemented with smooth utilization of computers in personnel training in the industrial field and school education as a core.

Personnel Training for Industrial Fields

At present, quality and quantity of information-related engineers (system engineers, senior programmers, and the like) are very poor. To cope with this situation, a model system--a high-information technology training system--utilizing CAI (Computer Aided Instruction) technology will be developed in order to train excellent information-related engineers efficiently, and high-grade information engineer training utilizing this system will be pushed forward. The CAI system is "a training system utilizing computers" and comprises CAI equipment (hardware, basic software, etc.) and courseware (training aids).

Examples of Training Utilizing the CAI System

Understanding of the operation in a computer from the time when programs are given to the time when outputs are obtained from a printing device and the like.

The operation of each device is explained at every step by fully utilizing animation and the like in addition to sentences and graphics.

Programming practice (COBOL...)

After an example of a program for a problem is explained, an exercise problem is given. The answer program is completed, with conversation by computer being made through a screen. The computer indicates the errors in the program inputted by the student and gives the advice (explanation of commands and the like) for the question to the student.

Detailed projects are as follows:

Establishment of CAI system specifications for information-processing engineer training; preparation of standard curriculums for information-processing engineer training; and promotion of spreading activity of those CAI systems.

Facilitation of Computer Utilization in School Education

In the rapid progress of information utilization, it is necessary that people in extensive fields in the country not feel reluctance in utilizing

(Reference 1)

Status of Computer Introduction to Schools in Three Countries

	(Rate of schools having one or more computers)
Japan:	Grade school 0.6 percent, Junior high school 3.1 percent, High school 56.4 percent (1983)
The United States:	Grade school 84.8 percent, Junior high school 91.8 percent, High school 93.9 percent (1984)
The United Kingdom:	Elementary school 43 percent, Middle school 100 percent, (1983)

[References 2, 3 not reproduced]

information equipment such as computers (promotion of information literacy). Therefore, the computers should be included in elementary schools so they can be a natural part of childhood experience. Education utilizing computers is expected as the effective means for diversifying the methods of education.

In order to promote the computer education in the future, it is necessary to establish the basic technological system as an infrastructure before the provision of hardware. Thus convenience for teachers should be improved, training of the teachers should be promoted and facilitated, and efficiency of software development and expansion should be realized.

Based on these viewpoints, the following measures are taken so as to smooth the computer utilization in the school education: development of support systems for preparing training aids; establishment of standard specifications for CAI systems used in school education; and research and development of CAI related basic technologies.

In the research and development of these projects, it is necessary that the opinions of educators be reflected and that flexible measures be taken in correspondence with the time and methods of the expansion of computer utilization in the schools. Therefore, a software development organization will be established for computer utilization in education under the auspices of both the Ministry of Education and MITI. The organization will be responsible for the research and development in these fields.

The support system for preparation of training aids is a system, by which courseware can be readily prepared in talking with display screens by persons who prepare training aids, without the need to learn special program languages, such as FORTRAN and BASIC.

Projects for Facilitating Software Production and Supply

Stable supply of high-quality software is a prerequisite for realizing high-information society. Owing to the drastic progress of information utilization and rapid speed of computers at present, however, demands for software are increasing rapidly. Its yearly growth rate has reached about 26 percent. On the other hand, the number of engineers for software development is always in short and their supply is limited. The annual growth rate of the number of software engineers is only 13 percent. As a result, the gap between the demand and supply of software will be expanded and it is expected that the shortage of software engineers will reach 600,000 by fiscal 1990. In addition, software costs in information-processing are constantly increasing, and software reliability requirements are becoming very strict.

Therefore, in the Information-Processing Promotion Association, which is the nuclear promoting organization of the software projects, excellent programs are being developed, data bases for these programs are being constructed, information is being provided and consultation is being carried out. Thus the circulation of the programs will be promoted.

The following projects will be deployed in detail:

(a) Promotion of development of general-purpose programs

Program development demands in the important fields (data bases, new media, security, CAD, etc.) are to be explored. Based on the program development demands, detailed programs to be developed are carefully selected, and the development is delegated, with the basic specifications being indicated. Thus the improvement in technological power of software firms is supported.

(b) Acceleration of circulation of general-purpose programs

Based on the results of the development of the general-purpose programs, the following circulation accelerating projects will be carried out.

In order to provide various kinds of information with regard to the general-purpose programs to the public extensively, information data bases for the general-purpose programs will be constructed and managed.

In order to spread and expand programs and the like for personal computers aiming at medium and small companies, expansion and support systems of general-purpose programs for the medium and small companies will be constructed and managed.

In order to aid the general public with respect to the general-purpose programs, a world trade fair will be held.

In order to free software development from hands-on workings, to greatly enhance the software productivity, which is said to be 4 percent annual growth at present and to improve the software reliability, the software-production industrializing project (Sigma Project) will be continuously promoted by the IPA.

Projects of the Information-Processing Promotion Association

Based on the Sigma Project, which was started in fiscal 1985, the integrated measures for smoothing software supply will be conducted by the following three projects utilizing the investment from the Special Industrial Investment Account.

(Financial Investment) Industrial investment: Y6.2 billion (Y2 billion)

Information-utilization training and personnel development promoting project (new)

General-purpose program development and circulation promoting project

Software-production industrializing project

(Budget) General-account projects of the Information-Processing Promotion Association: Y1.65 billion (Y2.35 billion)

Basic-technology investigation on information processing for education (new): Y220 million (0)

(Financial Investment) Improvement in software productivity

Japan Development Bank: Loan for enhancing information processing (highest-priority special interest): Within Y2.5 billion (within Y79 billion for information-utilization promotion)

Loan to (i) automation of software development and (ii) training projects and the like for software development engineers.

2. PROMOTION OF DATA BASE BUILDUP MEASURES

Data bases are one of the mainstays for supporting the information society together with hardware, software, and personnel. The data base buildup is a prerequisite of the information utilization. However, the data base buildup in our country greatly lags behind foreign countries. In order to implement sound programs of the information utilization in our country, the buildup of the data bases should be positively promoted.

From this point of view, the integrated data base buildup promoting projects such as follows will be carried out: establishment of the systems for smoothly providing the government-owned data to public; promotion of the buildup of public data bases; assistance to the buildup of the data bases in non-government fields; and so on.

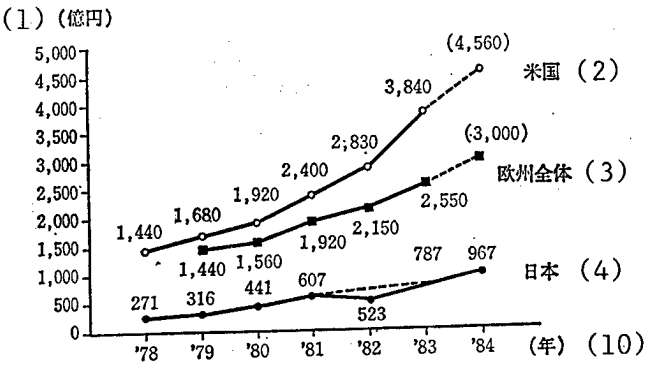
(1) Assistance to the Buildup of the Data Bases in Non-Government Fields

(Budget) Buildup and promotion (expansion) of the data base and information-providing service: Y110 million (Y12 million)

Study for development programs for important data bases such as the data bases in the leading technological fields like fine ceramics, new raw material, and so on, which will be constructed by the cooperation of industries, colleges, and government will be newly conducted. At the same time, the infrastructure for data base- and information-providing services such as the study on the data base- and information-providing service and the preparation of data base registers will be established.

(Tax System) Support for data base construction (tax system for promoting investment for equipment required for enhancing information-related infrastructure, new).

Selection of the 7 percent tax deduction or the 30 percent special depreciation in the initial fiscal year is approved for the procurement costs (including rental) of electronic computers, peripheral equipment, transmission equipment, and terminal equipment for constructing data base systems, which are acquired by data base companies.



(5) (注) 1. 1ドル=240円で計算 (6)
(7) 2. 日・欧についてはオンラインとバッチの合計
(8) 3. 米国はオンラインのみ
(9) (ソース) (財)日本情報処理開発協会推計 (日本は特定サービス産業実態調査より)

(Reference 4) Trend of Sales in Data-Base Service in Japan, the United States and Europe

Key:

1. (Y100 million)
2. The United States
3. Entire Europe
4. Japan
5. (Note)
6. 1. Computed on the basis of 1 dollar = Y240
7. 2. For Japan and Europe, sum of on-line bases and batch bases
8. 3. For the United States, only on-line bases
9. (Source): Estimation by Japan Information Processing Development Association (juridical foundation) (for Japan, data of fact-finding survey for specified service industries)
10. (Year)

(Financial Investment)

Loan for costs of data base construction (expansion of the limit of amount for promoting information-processing and communications systems, new): Within Y7.5 million (within Y79 million for information-utilization promotion)

Loan for non-equipment funds related to the costs of equipment and construction, which are acquired by companies conducting information providing service, when the data bases are constructed.

Investment for companies constructing infrastructural data bases (expansion of limit of amount for promoting information-processing and communications systems): Within Y7.5 billion (within Y79 billion for information-utilization promotion)

Investment for companies conducting information providing service, which construct "infrastructural data bases" required for the industrial and social activities and development of local societies.

(2) Construction of Public Data Bases and Promotion of Development of Data Base Related Technologies

(Budget)

Construction of public data bases

Construction and buildup of the public data bases will be continuously carried out with regard to the data bases required for promoting the international trade and industry administration as follows: technological data bases related to tests and researches conducted by the national government; patent data bases; economic and trading data bases for every country; and data bases related to medium and small companies for rationalizing the management of the medium and small companies.

- Technological data bases: Y100 million (Y100 million)

- Patent data bases: Y1.5 billion (Y1.5 billion)

-Economic and trading data bases for every country: Y100 million (Y100 million)

- Data bases for medium and small firms: Y290 million (Y220 million)

Research and development for data base systems for mutual operation of electronic computers (interoperable): Y840 million (Y20 million)

3. PROMOTION OF DEVELOPMENT OF INFORMATION-RELATED TECHNOLOGIES

In order that our economy and society may realize high-information society full of vitality and cope with the diversified industrial and social needs

flexibly in the future, technological development is indispensable.

For this purpose, the development of the following items and systems will be strenuously pushed forward: the fifth-generation computers, new function elements such as bionic elements, data base systems for mutual operation of electronic computers (interoperable), high-speed computing systems (supercomputers) for science and technologies, advanced social system, etc.

Development of the information-related technologies in nongovernment field will be promoted by utilizing the functions of investment and loan of the Infrastructural Technology Research Promotion Center, which was established on 1 October 1985.

(Budget)

1--Development of basic technologies of electronic computers (development of the fifth-generation computers): Y5.5 billion (Y4.8 billion)

The next fiscal year is the second year of the intermediate period (from fiscal 1985 to fiscal 1988) of the research and development of the fifth-generation computers. Functional design, detailed design, and so on are conducted for realizing inference subsystems, knowledge subsystems, and the like.

2--Research and development of new functional elements and so on (development of infrastructure techology for the next generation industries): Y1.5 billion (Y1.6 billion)

As new functional elements, by which high-information processing will become possible, research and development of super-lattice elements and three-dimensional-circuit elements will be continued.

Development of bionic elements will be newly started (budget: Y60 million)

3--Research and development of data base systems for mutual operation of electronic computers (interoperable) (large-scale project): Y840 billion (Y20 million)

High-degree data base systems having the following capability that will be required in 1990's will be developed: information, which is expressed by multi-media such as characters, graphics, images, and speech, can be handled between the different machines; i.e., interoperability can be secured.

4--Research and development of high-speed computing systems for science and technologies: Y2.9 billion (Y2.75 billion)

Full-scale development of high-speed computing systems, which are required for scientific and technological calculation such as processing of images sent from meteorological satellites, will be conducted.

5--Development of medical support systems: Y100 million (Y110 million)

Information systems aiming at the direct support of doctors' medical businesses will be continuously developed.

6--Projects of the Structural Technology Research Center

Investment and loan from the Special Industrial Investment Account: Y32 billion (Y10 billion)

4.ESTABLISHMENT OF INFRASTRUCTURE FOR INFORMATION UTILIZATION IN INDUSTRIES AND PROGRESS OF INFORMATION INDUSTRY

Information advancement in our country is the foundation of the information utilization for Japan's economy and society. From now on, however, it is necessary to promote information utilization beyond the framework of one company and also beyond the framework of one industry by forming inter-company information-processing systems.

For this objective, measures will be taken with respect to tax systems and financial investment for promoting the construction of the inter-company information systems. By utilizing "Cooperation Guidelines" based on the "Act of Information-Processing Promotion," which was amended in 1985, smooth information adaptation in the industry will be promoted in consideration for securing interoperability and the like.

In this case, the fact that the industrial and social activities greatly depend on information networks has been considered, and the following measures have been taken: "safety-counter-measure reference for electronic computer systems" has been presented; operating facilities of information-processing service business, where safety countermeasures for electronic computer systems have been enforced, have been approved. "System Inspection Reference" has been presented; and so on. In the future, it is necessary to improve stability and reliability of the information-processing system furthermore.

(Budget)

1--General-Account Projects of the Information-Processing Promotion Association (listed above): Y1.65 billion (Y2.35 billion)

2--Promotion of safety countermeasures in information-processing services: Y12 million (Y12 million)

(Tax System)

1--Tax system for accelerating investment on equipment for enhancing information-utilization infrastructure (new)

In order to implement a high-grade industrial structure, vitalization of industries and high-information society, which will bring about pleasant and enriched national life, construction of the systems, which will become the

infrastructure of the high-information society, i.e., the exchange of information-processing systems between companies will be promoted. From this point of view and also from the viewpoint of aiding the expansion of domestic demands, which is the most important problem for our country at present, the following tax system will be established: 7 percent tax deduction or special depreciation of 30 percent in the initial year can be selected for the procurement costs (including rental) of electronic computers, peripheral equipment, and transmission equipment, which are related to inter-company information-processing systems.

2--Reduction in real estate tax related to facilities and the like for computer-safety countermeasures (new)

The tax system, by which the tax basis for the real estate is made to be three-fourths the actual value for 3 years only from fiscal 1986, will be established with respect to the buildings and the specified equipment, upon which measures are taken in compliance with the "Safety Countermeasure Reference for Electronic Computer Systems."

(Financial Investment)

1--Promotion of Information-Processing and Communications Utilization

Loan from Japan Development Bank with special interest: Y7.5 billion (within Y79 billion for information-promotion utilization)

Procurement costs of equipment related to the system, which are to become the basis for promoting the information utilization in industries such as follows will be loaned: (a) on-line information-processing systems among a plurality of companies; (b) on-line information-processing systems constructed by information-processing-service companies and information-providing-service (data base service) companies; (c) highly social systems for medical, transportation, and disaster preventing organizations and so on; (d) so-called VAN and information-processing type CATV; (e) VIDEOTEX systems; and (f) local-area promotion system (new-media community).

In fiscal 1986, the conventional system setup is expanded, and the leasing business is added. In addition, the highest priority special interest will be applied, when on-line information-processing systems, in which safety countermeasures are adopted, will be introduced.

2--Implementation of high-grade information processing

Loan from Japan Development Bank: Y2.5 billion (within Y79 billion for information-utilization promotion)

Equipment funds will be loaned when information-processing service companies and the like carry out the following businesses: (a) training business for information-processing engineers; (b) automation of the business for improving information processing efficiency, strengthening technological development and improving working conditions and manpower saving business; and (c)

construction of information-processing systems among a plurality of companies. With respect to (c) above, non-equipment fund will be loaned.

3--Improvement of reliability of information equipment and the like

Loan from Japan Development Bank with special interest: Y11 billion (within Y79 billion for information-utilization promotion)

Rapid improvement in reliability and performance of equipment, parts, materials and the like related to information, which are to become the infrastructure of high-information society, is indispensable. Therefore, funds for improving reliability in manufacturing equipment and the like will be loaned.

4--Promotion of electronic computers (loan for JECC)

Loan from Japan Development Bank: Y65 billion (within Y79 billion for information-utilization promotion)

Funds required for the rental business of electronic computers carried out by Japan Electronic Computer Co., Ltd., will be loaned.

5--Financial measure for promoting information processing (financial bond accepting measure): Y4 billion (Y3 billion)

Funds will be loaned at low interest (7 percent) to information-processing service companies (including software companies) for the following activities: (a) introduction of electronic computers; (b) development and introduction of programs; (c) training of engineers; and (d) long-term working funds. The same loan with low interest (7 percent) will be provided for companies for (a) equipment funds and non-equipment funds for developing programs and (b) long-term funds for the training of engineers within the company.

6--Government guaranteed loan for low-interest finance business conducted by the Information-Processing Promotion Association (new): Y1.5 billion (0)

The government will give warranty to the loans for the original funds of low-interest finance business conducted by the IPA for the funds of system design and program development related to joint information systems within one industry or between different industries.

5. INFORMATION UTILIZATION IN LOCAL AREAS

In order to implement balanced information utilization throughout the country, difference in information utilization among local areas should be corrected so as to develop local areas.

For this purpose, the following measures will be taken: concept for information utilization in local areas will be established; the way the information utilization should be for aiding the balanced advancement of local areas will be presented; and the new-media community concept, which is intended for developing and spreading various information systems matching the needs of local communities, will be further promoted. With respect to the new-media community concept, model areas will be added and the application-developing-area system will be established so that financial and tax measures will be taken. Thus the information-utilization infrastructure in local areas will be built up and expanded.

(Budget)

1--Information-utilization system developing project for model communities, etc. (expansion): Y70 million (Y74 million)

For further drive of the new-media concept, model areas will be added (seven areas), and the application-developing-area system, in which information systems will be introduced in applied and developed forms, will be established.

2--Establishment of concept for information utilization in local areas (new): Y9 million (0)

In order to present the way the information utilization should be for aiding the balanced local area development, the concept for the information utilization in local areas will be established by each Regional Bureau of International Trade and Industry.

(Tax System) Reduction in real-estate tax of juridical persons promoting information utilization in local areas (new)

The tax system, by which the tax basis will be reduced to one-half for 3 years after acquisition, will be estalished with respect to the specified real estate, which will be used for the construction and operation of the information systems conducted by the companies promoting information utilization in local areas.

(Financial Investment)

1--Investment to the companies promoting the new-media community concept from the Infrastructural Technology Research Promotion Center: Within Y15 billion (within Y2 billion)

2--Promotion of information utilization in local areas

Loan from North East Finance Corp.: Y2 billion (0) (within Y135 billion)

3--Buildup of infrastructure of information utilization in local area (new)

Loan from North East Finance Corporation: Y2 billion (0)

Juridical persons, which develop software, are added to the objects of loan of North East Finance Corp., and the equipment funds and the long-term working funds for software developing business and the training business for information-processing engineers will be loaned or invested.

4--Promotion of the implementation of information-processing and communications systems

Special loan from Japan Development Bank: Y7.5 billion (within Y79 billion for information-utilization promotion)

5--Promotion of the implementation of information-processing and communications systems (expansion)

Investment from Japan Development Bank: Within Y7.5 billion (within Y79 billion for information-utilization promotion)

Investment will be made to the third sectors which will construct and operate the information systems in application developing areas.

6. INTERNATIONAL DEPLOYMENT OF INFORMATION UTILIZATION

For international deployment of information utilization, cooperation with developing countries including Pacific areas will be positively carried out.

(Budget)

1--Establishment of integrated information-utilization concept for ASEAN countries (new): Y30 million

The integrated information-utilization concept for ASEAN countries will be established in association with the countries concerned, and cooperation in efficient progress of the information utilization in industries and society will be promoted.

2--Projects of the International Information-Utilization Cooperation Center: Y240 million (within Y212 million)

(a)Reinforcement of training and guidance related to information utilization in each country

In addition to existing three courses, i.e., an instructor course, an SE course, and a personal computer course, an OA course (office automation technology, application systems in management, instruction methods, techniques for promoting information utilization, etc.; 10 persons, 6 months, one time) will be newly established, and engineers, who will become cadre for promoting the information utilization in the development countries will be trained.

(b)Assistance to the technological guidance related to the buildup of the information systems in developing countries.

Assistance will be given to the dispatch of specialists from Japan and guidance when developing countries will introduce and operate the equipment and systems related to information.

3--Research and development of computer aided translation systems between neighboring countries (a large project of ODA, new): Y38 million (0)

Research and development of automatic translation systems between neighboring countries will be started in order to promote smooth technological cooperation and cultural exchange with ASEAN countries, to transfer software technologies and to establish information-processing technologies in native languages. As applications systems, data base networks having computer translation function will be studied.

7. INFORMATION UTILIZATION IN MEDIUM AND SMALL COMPANIES

In order to overcome the difference in information utilization between medium and small companies and large companies resulting from the advance in the information utilization and to make the most of the progress of information utilization positively, the integrated information-utilization projects for medium and small firms will be promoted as follows: reinforcement of the guidance functions of the Local Medium and Small Firm Information Centers; buildup of the systems for expansion of capability upgrading business, equipment lease business and the like; promotion of buildup of information networks for medium and small companies; and establishment of information-utilization advisor systems.

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